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Restoration of mitochondria cristae in live microscopy images

Inria

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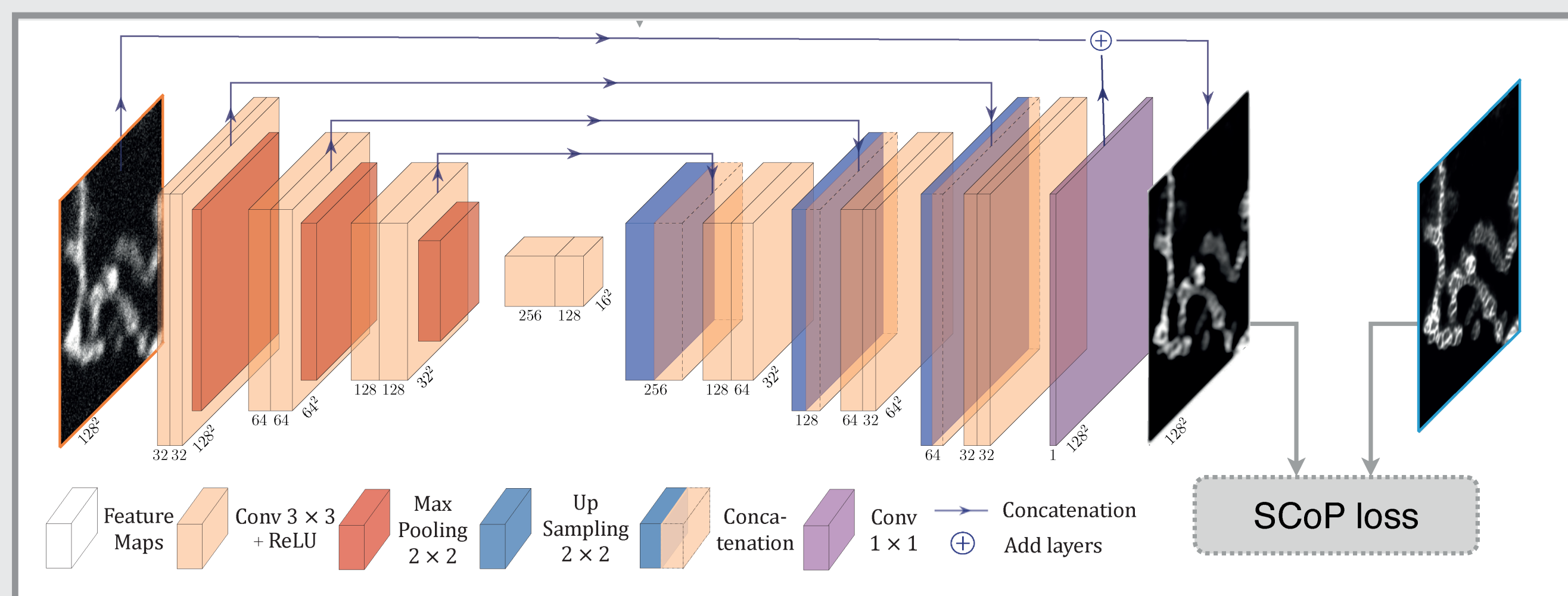
Abstract

Mitochondria play an essential role in the life cycle of eukaryotic cells. However, we still don't know how their ultrastructure, like the cristae of the inner membrane, dynamically evolves to regulate these fundamental functions, in response to external conditions or during interaction with other cell components. Although high-resolution fluorescent microscopy coupled with recently developed innovative probes can reveal this structural organization, their long-term, fast and live 3D imaging remains challenging. To address this problem, we have developed a convolutional neural network to restore mitochondrial cristae in low spatial resolution microscopy images. Depending on the conditions of use indicated, our method works well on broad microscopy modalities (STED, Live-SR and LLSM). It is ultimately applied in the context of mitochondrial network dynamics during interaction with endo/lysosomes membranes.

Framework

Training step

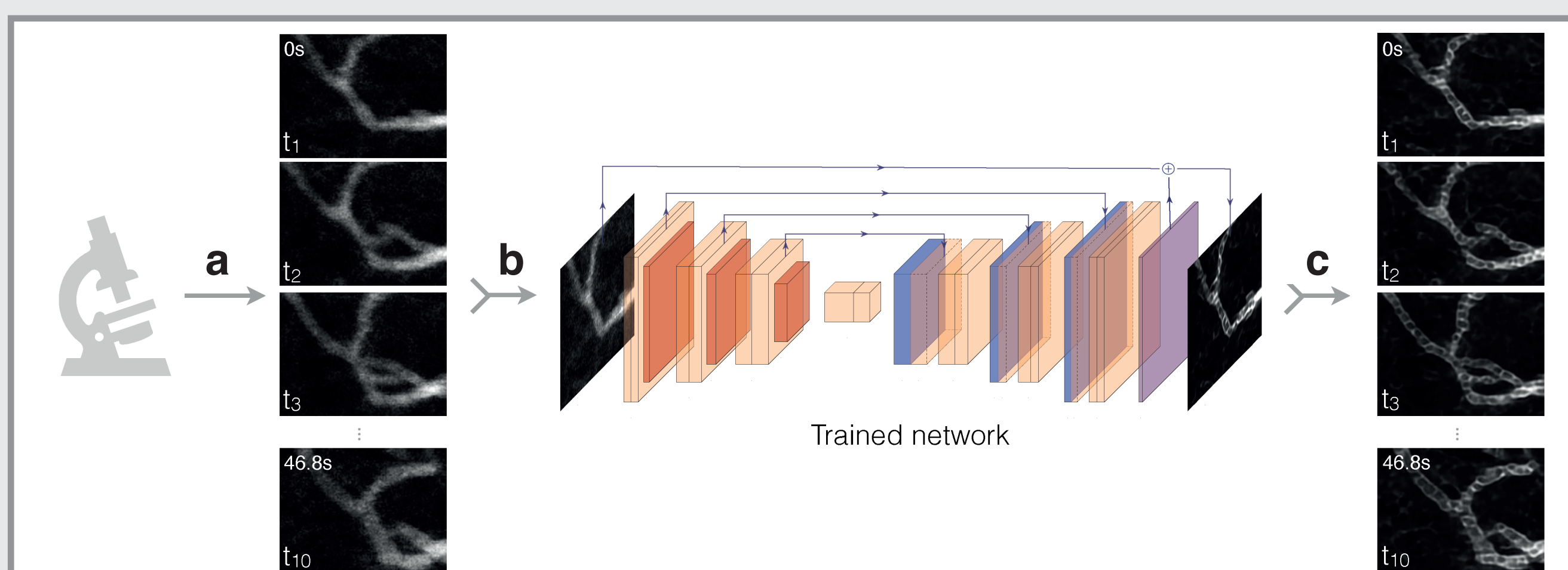
Our CNN is trained from 2D STED images using a novel loss specifically designed for cristae restoration



$$SCoP(y, \hat{y}) = \frac{1}{N^2} \sum_{i=1}^N \sum_{j=1}^N \left(\frac{1 - SSIM_{y, \hat{y}}^{\text{map}}(i, j)}{2} \right)^{\gamma_{i, j}}$$

- y : target image
- \hat{y} : restoration
- $SSIM_{y, \hat{y}}^{\text{map}}$: map of the local structural similarity values for corresponding pixels between the images y and \hat{y}
- $\gamma_{i, j}$: prioritization of the restoration of specific regions of interest. It is equal to 1 if the pixel (i, j) belongs to a mitochondrion, 4 otherwise.

Inference step

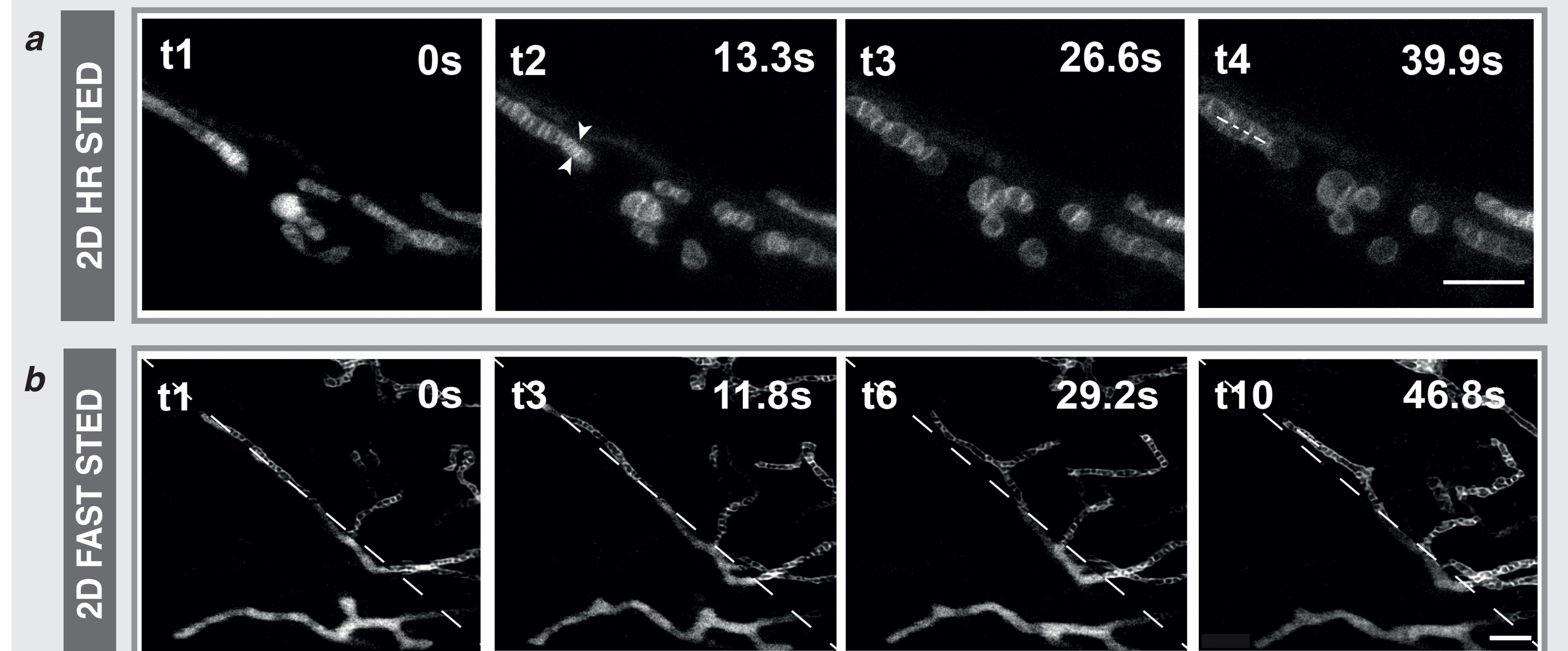


(a) long-term and fast acquisition with low illumination of live mitochondria. Note that if the training was performed on degraded STED images, the inference can be made on other microscopy modalities (e.g., Live-SR and LLSM)

(b) frame-by-frame restoration of the acquired sequence by our previously trained network, allowing observation of the mitochondrial cristae dynamics at high resolution

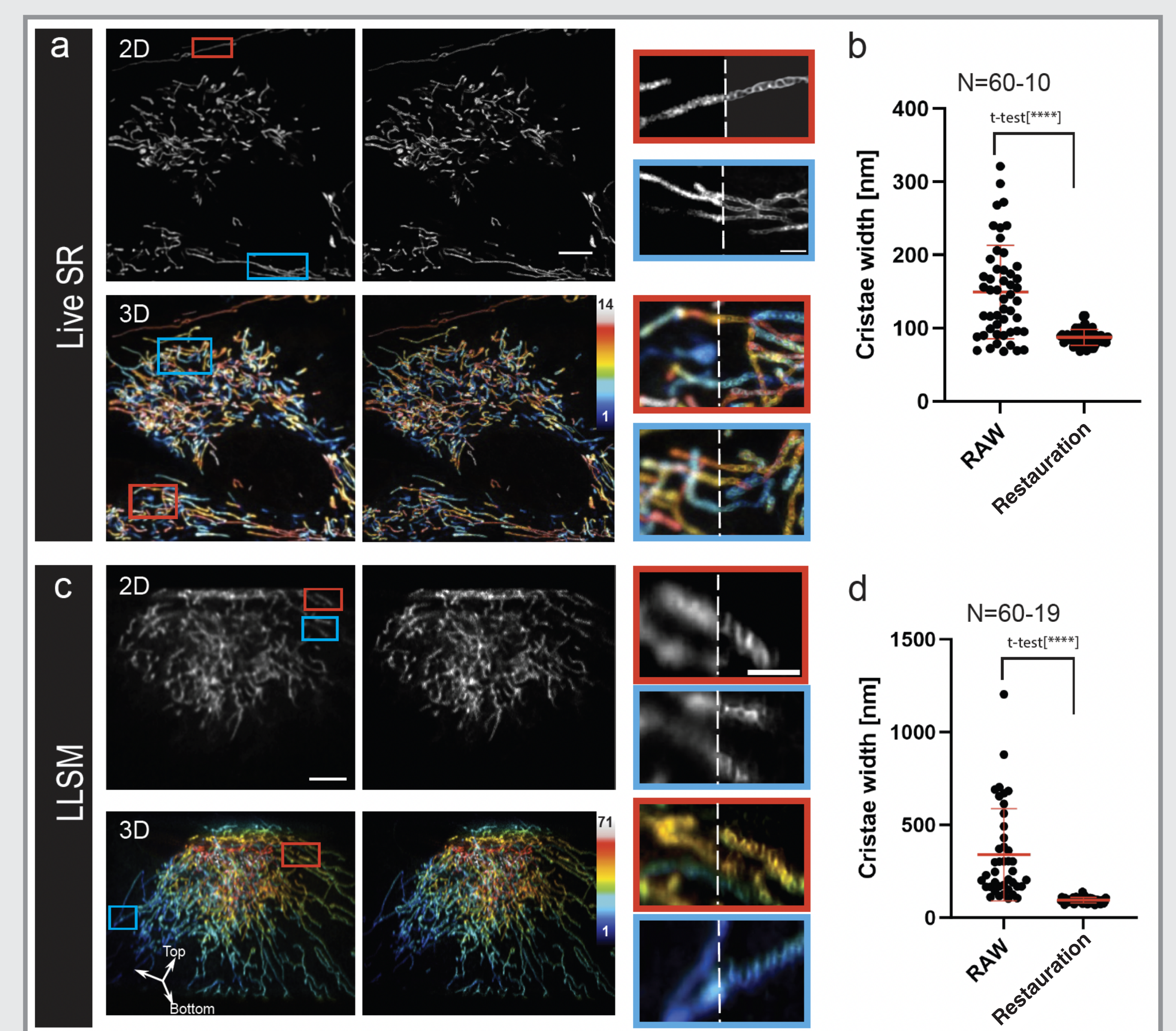
Results

Restoration of mitochondria cristae from low resolution 2D live STED



2D live STED imaging of RPE1 cells labeled with PKMITO-Orange. (a) Time series ($\Delta t \sim 13$ s) using 2D high-resolution (HR) STED. Pixel size is 25 x 25 nm. Observation of phototoxic damage illustrated by the swelling of the mitochondria. (b) Time series of 2D Fast STED, improving the time delay between time points ($\Delta t \sim 5.9$ s) and reducing mitochondrial damage. Each thumbnail is diagonally divided for raw 2D Fast STED images (bottom-left part) and after treatment with our method (top-right). Scale Bars are: 2 μ m.

Enhancement of cristae width resolution in 3D and 3D+live imaging



(a, c) 2D plane (top) and 3D MIP (bottom) of cells labeled with PKMITO-Orange, acquired with a SD microscope with a Live-SR module for (a) and a LLSM microscope in (c), before (left) and after restoration (right). Thumbnails are zoomed areas corresponding to the insets (red and blue) and are composites of raw and restored images. Color scale bar indicates the bottom to top position of mitochondria. (b, d) Measurements of cristae widths for Live SR in (b) and LLSM in (d).

Conclusions

- Reveals cristae in images taken with low photon illumination, enabling clearer visualization and analysis of mitochondria cristae in living cells without interfering with the natural behavior of mitochondria
- Works well on broad microscopy modalities (STED, Live-SR and LLSM)
- Makes it possible to track the evolution of mitochondrial cristae morphology over time, during interactions with other membrane components of the cell, or under extracellular conditions that mimic various pathological or stress situations