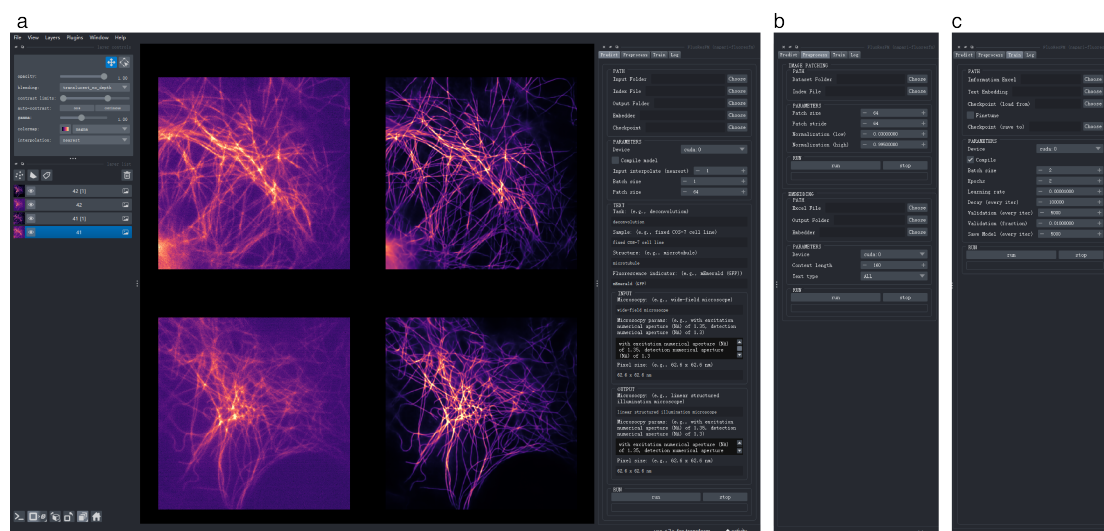


Supplementary Information

Supplementary Figures



Supplementary Fig. 1 | Interactive interface of the napari plugin for FluoResFM. The developed napari plugin can be used to implement data preprocessing, model training, and model prediction. **a**, The widget used for restoring low-quality images using a pre-trained FluoResFM model. Two pairs of representative low-quality input and high-quality restored images are shown in the viewer. **b**, The widget used for data preprocessing, which can perform image patching and text embedding. **c**, The widget used for model training and fine-tuning.

Supplementary Tables

Supplementary Table 1 | Overview of the training dataset details. The image restoration task, imaging object, imaging device (microscopy), and the download link of each dataset are provided. DN, denoising; DCV, deconvolution; SR, super-resolution; CCP, clathrin-coated pit; ER, endoplasmic reticulum; MT, microtubule; Mito, mitochondria; NCC, neural crest cell; NPC, nuclear pore complex; BPAE, bovine pulmonary artery endothelial cell; WF, wide-field; SIM, structured illumination microscopy; STED, stimulated emission depletion microscopy.

Dataset	Task	Imaging object	Microscopy	Link
BioSR	DN, DCV, SR	CCP	WF, SIM	https://figshare.com/articles/dataset/BioSR/13264793
		ER	WF, SIM	https://figshare.com/articles/dataset/BioSR/13264793
		F-actin	WF, SIM	https://figshare.com/articles/dataset/BioSR/13264793
		MT	WF, SIM	https://figshare.com/articles/dataset/BioSR/13264793
BioSR+	DN	CCP	WF	https://zenodo.org/records/7115540
		ER	WF	https://zenodo.org/records/7115540
		F-actin	WF	https://zenodo.org/records/7115540
		MT	WF	https://zenodo.org/records/7115540
		myosin-IIA	WF	https://zenodo.org/records/7115540
CARE	DN	nuclei (planaria)	confocal	https://doi.org/10.17617/3.FDFZOF
		nuclei (Tribolium)	multi-photon	https://doi.org/10.17617/3.FDFZOF
	SR	histone (Drosophila)	light-sheet	https://doi.org/10.17617/3.FDFZOF
		nuclei (retina)	confocal	https://doi.org/10.17617/3.FDFZOF
		nuclear-envelope (retina)	confocal	https://doi.org/10.17617/3.FDFZOF
		nuclei/membrane	two-photon	https://doi.org/10.17617/3.FDFZOF
	DCV	granule	WF	https://doi.org/10.17617/3.FDFZOF
		tubulin	WF	https://doi.org/10.17617/3.FDFZOF
DeepBacs	DN	nucleoid	confocal	https://github.com/HenriquesLab/DeepBacs/wiki
		MreB	confocal	https://github.com/HenriquesLab/DeepBacs/wiki
	DCV, SR	membrane (E. coli)	WF, SIM	https://github.com/HenriquesLab/DeepBacs/wiki
		membrane (S. aureus)	WF, SIM	https://github.com/HenriquesLab/DeepBacs/wiki
W2S	DN, DCV, SR	Mito	WF, SIM	https://zenodo.org/records/3895807
		lysosome	WF, SIM	https://zenodo.org/records/3895807
		F-actin	WF, SIM	https://zenodo.org/records/3895807
SR-CACO-2	DN, SR	histone	confocal	https://github.com/sbelharbi/sr-caco-2
		survivin	confocal	https://github.com/sbelharbi/sr-caco-2
		tubulin	confocal	https://github.com/sbelharbi/sr-caco-2
FMD	DN	nuclei (BPAE)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		F-actin (BPAE)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		Mito (BPAE)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		NCC (zebrafish)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		chromosome (mice)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		chromosome (mice)	two-photon	https://github.com/yinhaoz/denoising-fluorescence
		nuclei (BPAE)	two-photon	https://github.com/yinhaoz/denoising-fluorescence
		F-actin (BPAE)	two-photon	https://github.com/yinhaoz/denoising-fluorescence
		Mito (BPAE)	two-photon	https://github.com/yinhaoz/denoising-fluorescence
		nuclei (BPAE)	WF	https://github.com/yinhaoz/denoising-fluorescence
		F-actin (BPAE)	WF	https://github.com/yinhaoz/denoising-fluorescence
		Mito (BPAE)	WF	https://github.com/yinhaoz/denoising-fluorescence
VMSIM5	DCV, SR	Mito	WF, SIM	https://zenodo.org/records/3295829
RCAN-in	DCV, SR	MT	confocal, STED	https://zenodo.org/records/4624364#.YF4lBa9Kgal
		NPC	Confocal, STED	https://zenodo.org/records/4624364#.YF4lBa9Kgal
	DN	golgi	SIM	https://zenodo.org/records/4624364#.YF4lBa9Kgal

18 **Supplementary Table 2 | Overview of the external evaluation datasets.** DN, denoising; DCV, deconvolution; SR,
 19 super-resolution; MT, microtubule; Mito, mitochondria; ER, endoplasmic reticulum; CCP, clathrin-coated pit; WF,
 20 wide-field; SIM, structured illumination microscopy; iSIM, instant structured illumination microscopy.

Dataset	Task	Imaging object	Microscopy	Link
SIM	DCV	F-actin	WF, SIM	http://www.cellimagelibrary.org/images/7052
		MT	WF, SIM	http://www.cellimagelibrary.org/images/36797
VMSIM3	DCV, SR	Mito	WF, SIM	https://zenodo.org/records/3295829
VMSIM488	DCV	microsphere	WF, SIM	https://zenodo.org/records/3295829
VMSIM568	DCV	microsphere	WF, SIM	https://zenodo.org/records/3295829
VMSIM647	DCV	microsphere	WF, SIM	https://zenodo.org/records/3295829
RCAN-ex	DN	F-actin	iSIM	https://zenodo.org/records/4624364#.YF4lBa9Kgal
		ER	iSIM	https://zenodo.org/records/4624364#.YF4lBa9Kgal
		lysosome	iSIM	https://zenodo.org/records/4624364#.YF4lBa9Kgal
		Mito	iSIM	https://zenodo.org/records/4624364#.YF4lBa9Kgal
		MT	iSIM	https://zenodo.org/records/4624364#.YF4lBa9Kgal
BioTISR	DN, DCV, SR	CCP	WF, SIM	https://zenodo.org/records/14760518
		F-actin	WF, SIM	https://zenodo.org/records/14760518
		lysosome	WF, SIM	https://zenodo.org/records/14760518
		MT	WF, SIM	https://zenodo.org/records/14760518
		Mito	WF, SIM	https://zenodo.org/records/14760518

21
 22 **Supplementary Table 3 | Overview of datasets used for segmentation performance evaluation.** The “task” refers
 23 to the applied restoration task before segmentation using Nellie or Cellpose-SAM. DN, denoising; DCV,
 24 deconvolution; SR, super-resolution; CCP, clathrin-coated pit; Mito, mitochondria; BPAE, bovine pulmonary artery
 25 endothelial cell; WF, wide-field; SIM, structured illumination microscopy.

Dataset	Task	Imaging object	Microscopy	Link
CARE	DN	nuclei (planaria)	confocal	https://doi.org/10.17617/3.FDFZOF
		nuclei (Tribolium)	multi-photon	https://doi.org/10.17617/3.FDFZOF
	SR	nuclei/membrane	two-photon	https://doi.org/10.17617/3.FDFZOF
DeepBacs	DN	nucleoid	confocal	https://github.com/HenriquesLab/DeepBacs/wiki
	DCV	membrane (E. coli)	WF, SIM	https://github.com/HenriquesLab/DeepBacs/wiki
		membrane (S. aureus)	WF, SIM	https://github.com/HenriquesLab/DeepBacs/wiki
SR-CACO-2	DN, SR	histone	confocal	https://github.com/sbelharbi/sr-caco-2
FMD	DN	nuclei (BPAE)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		F-actin (BPAE)	confocal	https://github.com/yinhaoz/denoising-fluorescence
		Mito (BPAE)	confocal	https://github.com/yinhaoz/denoising-fluorescence
BioTISR	SR	CCP	WF, SIM	https://zenodo.org/records/14760518
		F-actin	WF, SIM	https://zenodo.org/records/14760518
		lysosome	WF, SIM	https://zenodo.org/records/14760518
HL60	DN, DCV	nuclei	confocal	https://bbbc.broadinstitute.org/BBBC024
Scaffold-A549	DN	nuclei	confocal	https://github.com/Kaiseem/Scaffold-A549
GranuSEG	DN	nuclei	confocal	https://cbia.fi.muni.cz/datasets/
ColonTissue	DCV	nuclei	confocal	https://cbia.fi.muni.cz/datasets/

27 **Supplementary Table 4 | Detail settings of FluoResFM and comparison models during training and fine-tuning.**
 28 As UniFMIR model can only be trained with a batch size of 1, it used more training iterations to go through all the
 29 training patches.

	Model	Optimizer	Initial learning rate	Patch size	Batch size	Total training iterations
Fig. 1-6	FluoResFM	AdamW	1×10^{-5}	64×64	16	700,000
Fig. 2,3,5	UniFMIR	AdamW	1×10^{-4}	64×64	1	4,300,000
Extended Data Fig. 1	CARE:CCP	AdamW	1×10^{-4}	64×64	16	700,000
Extended Data Fig. 1	CARE:ER	AdamW	1×10^{-4}	64×64	16	700,000
Extended Data Fig. 1	CARE:MT	AdamW	1×10^{-4}	64×64	16	700,000
Extended Data Fig. 1	CARE:Mix	AdamW	1×10^{-4}	64×64	16	700,000
Fig. 5	CARE	AdamW	1×10^{-4}	64×64	16	32,000
Fig. 5	DfCAN	AdamW	1×10^{-4}	64×64	16	32,000
Fig. 5	FluoResFM (ft)	AdamW	1×10^{-5}	64×64	16	32,000
Fig. 5	UniFMIR (ft)	AdamW	1×10^{-4}	64×64	1	36,600