Cell Cycle Detection Using Phase Imaging with Computational Specificity (PICS)

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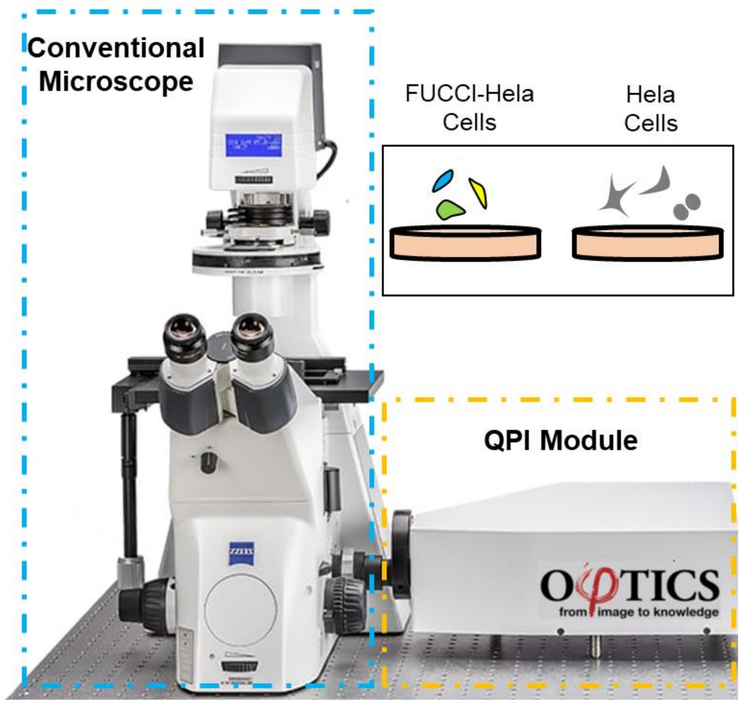
**Equal contributions*

Abstract

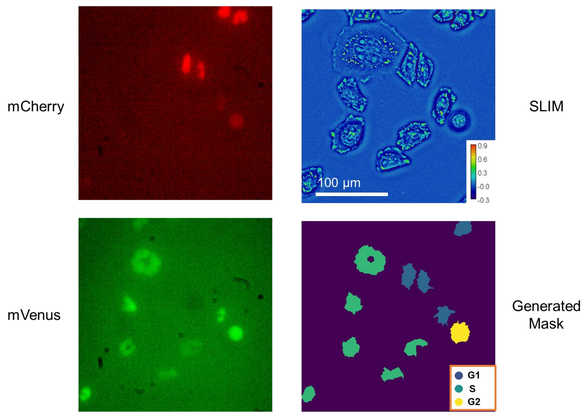
Quantitative phase imaging (QPI), with its capability to capture intrinsic contrast within transparent samples, has emerged as an important imaging method for biomedical research. However, due to its label-free nature, QPI lacks specificity and, thus, often faces limitations in informing about biological mechanisms. In our previous works, we have proposed phase imaging with computational specificity (PICS) as a novel AI-enhanced imaging approach that advances QPI by utilizing deep learning for specificity. Here we demonstrate that PICS can be applied to identify different phases of the cycle associated with unlabeled cells. Using this information, we can study individual cell behavior and cellular dry mass change across various cell cycle phases, without fluorescent tags or cell synchronization. The cell cycle information is traditionally obtained by fluorescence microscopy with markers like Fluorescence Ubiquitin Cell Cycle Indicator (FUCCI). Although FUCCI is a valuable marker in cell biology, utilizing it requires complex and expensive sample preparation, while the fluorescence imaging itself suffers from photobleaching and phototoxicity. Our work showed that using deep learning, we can train a neural network to accurately and efficiently predict the cell cycle phase (G1, S, M, and G2) for each cell. Unlike some of the previous applications of machine learning to cell cycle study, our method can be applied to images with large cell clusters and can classify the interphase: G1, S, and G2 for the whole image.

System Setup

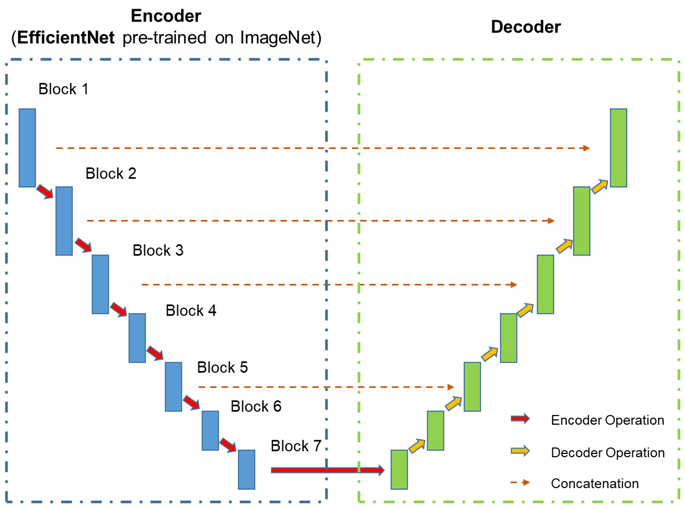


- Time lapse imaging of both FUCCI-Hela cells and regular Hela cells
- Acquiring three channels simultaneously (Phase, mCherry, and mVenus)

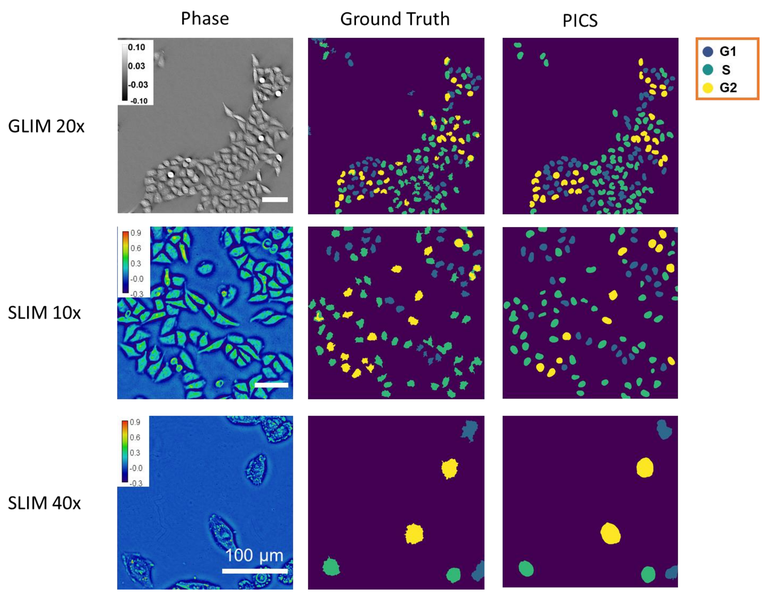
Deep Learning



- Adaptive thresholding was utilized to generate the ground truth label.



- An EfficientNet-based U-Net was applied, where the input are QPI images, and output are corresponding cell cycle label maps.
- The model was optimized using Adam optimizer against a weighted sum of Dice loss and binary focal loss



- PICS works across different imaging modality and magnification.

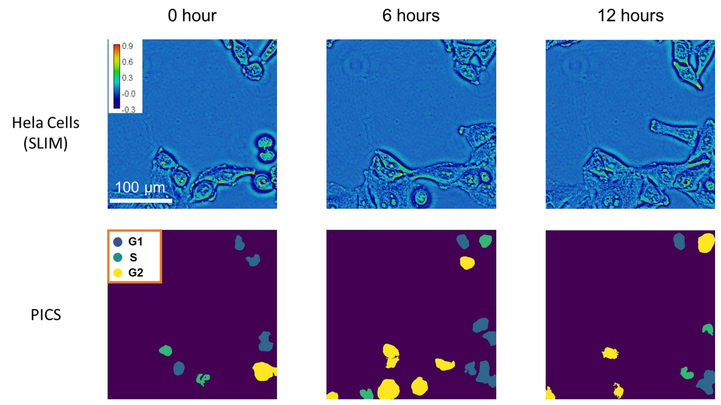
Evaluation

- A post-processing step was introduced on the model prediction to enforce particle-wise consistency and remove particles that are too small to be classified as cell nuclei.
- The area filter size was chosen on the validation dataset, aiming to maximize the F-1 score of the prediction. Once the size was chosen, it was fixed and applied to all images in the test dataset..

- The precision and recall scores for each model were computed on the test dataset. The scores reported here are based on number of cells.

	G1		S		G2	
	Precision	Recall	Precision	Recall	Precision	Recall
GLIM 20x	58.92%	75.65%	50.85%	65.94%	64.78%	60.11%
SLIM 10x	65.70%	83.24%	65.30%	68.45%	60.06%	58.40%
SLIM 40x	73.44%	81.87%	61.37%	67.93%	69.84%	80.68%

- The model trained on FUCCI-Hela cells can also be applied to regular Hela cells to infer the cell cycle phase.



Reference and Funding

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2. Y. Park, C. Depeursinge, and G. Popescu, "Quantitative phase imaging in biomedicine," Nature Photonics, vol. 12, no. 10, pp. 578-589, 2018.
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