Deep learning models capture high-dimensional features for cell morphology analysis from brightfield images

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KEY POINTS

- Morphology is a fundamental cell property associated with identity, state, & function, but there is a need for high-dimensional, unbiased, & quantitative assessment.
- The REM-I platform combines label-free brightfield imaging, deep learning, morphometrics, & gentle cell sorting to leverage high-dimensional single cell morphology as a biological readout.
- Applications include high-throughput sample characterization, disease detection/enrichment, drug/functional screening, & multi-omic integration.

INTRODUCTION

- Deepcell's **H**uman **F**oundation **M**odel **(HFM)** is a hybrid architecture that combines self-supervised learning (SSL) & morphometrics (computer vision) to extract 119 dimensional embedding vectors representing cell morphology from high-resolution REM-I cell images. **(Fig. 1)**
- SSL produces a foundation model with high generalization capabilities that enables hypothesis-free sample exploration and efficient generation of application-specific models.
- Computer vision extracts features that represent measurable concepts and improves model interpretability.
  - e.g., cell size, shape, texture, intensity

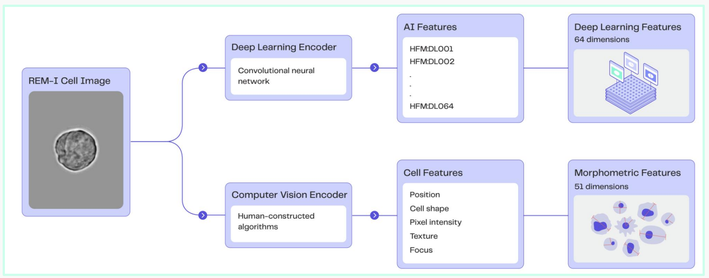


Figure 1. HFM is a feature extractor. Features of cell images are encoded into high-dimensional numerical vectors.

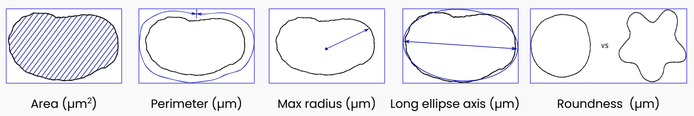
METHODS

→ Real-Time Image Processing

- Cells are detected and tracked as they flow through a microfluidic channel.
- Raw brightfield images of single cells are captured at up to 10,000 frames/sec and corrected for per-pixel variation in background offset, camera gain, & illumination.
- Each cell is segmented, cropped, & centered; the background normalized to a standard value.

→ Morphometric Features

A



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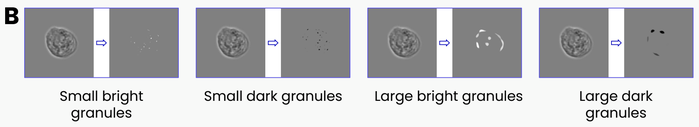
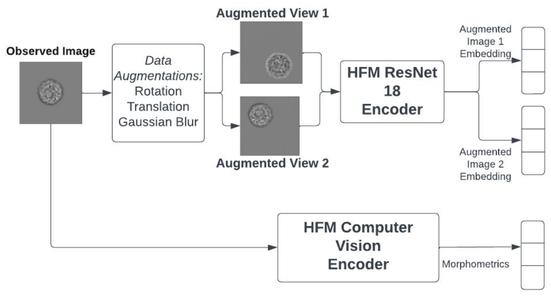


Figure 2. Examples of morphometric features. (A) Representative images showing 5 of 14 features describing cell shape and size. **(B)** Representative images showing 4 of 41 features describing pixel intensity and texture. Shown are morphometrics that describe size and intensities of "granules", which relate to cellular structures like vesicles.

METHODS cont.

→ Image feature extraction and classification architecture

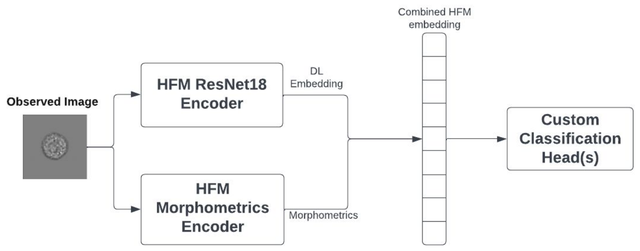
A



B

Invariance Loss	The distance between two embeddings from augmented images of the same cell is minimized.
Variance Loss	The variance of each embedding dimension over a training batch of images is maintained above a threshold.
Covariance Loss	The covariances between pairs of embedding dimensions over a training batch of images are minimized.
Morphometrics Decorrelation	The covariances between pairs of embedding and morphometric dimensions over a training batch of images are minimized.

C



D

Backbone deep learning model	ResNet 18
Model parameters	~11 million
Training data	
• Cell images	4,013,508
• Imaging runs	814
• Biological samples	35
Embedding dimensions	119 total 64 AI + 55 morphometrics
Forward pass latency (Nvidia T4 GPU, batch size 8)	0.95 ms/ image

Figure 3. Deepcell HFM training and inference architectures. (A) HFM training architecture. The backbone model, which extracts image features, is based on the ResNet18 convolutional deep neural network architecture. Training combines VICReg self-supervised learning, which learns image features without labels, with orthogonal morphometric features to improve model performance and interpretability. **(B)** Loss terms minimized during HFM training. **(C)** HFM evaluation architecture. The ResNet18 backbone trained in (A) and the morphometric feature encoder are applied along with custom trained classification heads to generate embedding vectors and classify cells. Calculations are performed on the REM-I instrument using Nvidia A6000 GPUs, Intel Xeon CPUs, and a custom FPGA to identify and sort cells in realtime. **(D)** HFM hyperparameters, training dataset details, and inference latency.

→ Model performance evaluation

HFM performance was evaluated using two simple datasets comprising multiple known cell types mixed *in silico*. For each dataset, a random forest classifier head was trained on HFM embeddings to predict cell class and evaluated using an independent set of images.

- **Figure 4:** mixture of four synthetic cell types ranging from 20-40 μm diameter that simulate cell features (used as a reference control sample)
  - Classification accuracy is 100% with several highly interpretable features driving classification.
- **Figure 5:** mixture of 6 μm beads and three cancer cell lines
  - Classification accuracy is high with biological samples of similar size distributions and features.

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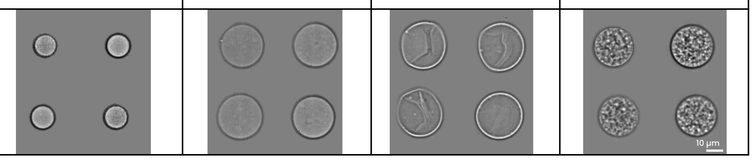
RESULTS.

A

Cell Class	Small	Large w/ particles	Large collapsed	Large w/ granules
Diameter	12 - 15 μm	23 - 27 μm	25 - 31 μm	20 - 26 μm
Training images	7,266	5,677	4,254	7,543
Test images	7,173	5,650	4,339	7,578
Example Images				

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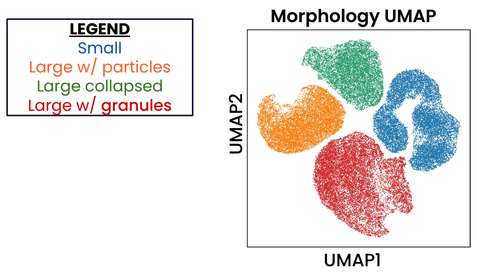

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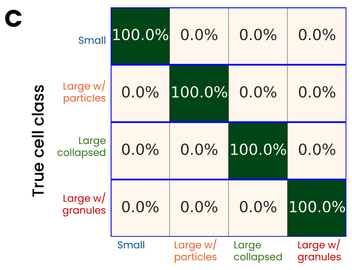

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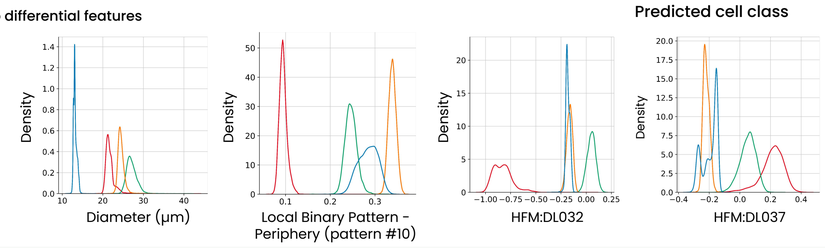
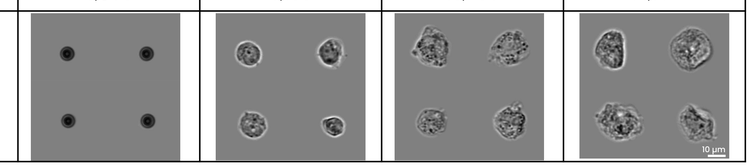


Figure 4. Evaluation of HFM synthetic cell classification. Synthetic cells with diverse structural features were imaged on the REM-I platform. **(A)** Table of cell classes, number of images used for training and testing, & representative images of each class. **(B)** Morphology UMAP of HFM embeddings colored by ground truth. **(C)** Confusion matrix: HFM predicts synthetic cell class with 100% accuracy in all 4 classes. **(D)** Top differential morphometric and deep learning features. Utilizing both AI-derived features and computer vision features enhances model explainability.

A

Cell Class	Bead	Jurkat	A375	Caov-3
Training images	12,561	26,593	16,018	16,427
Test images	3,866	6,150	15,256	14,712
Example Images				

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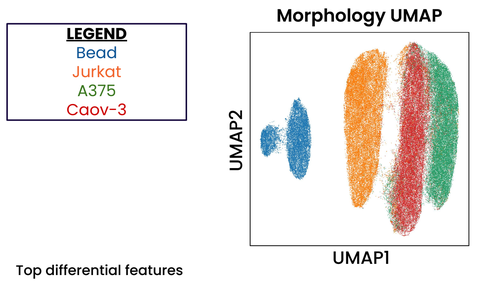

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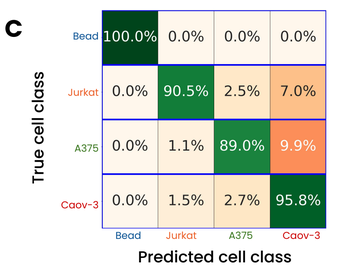

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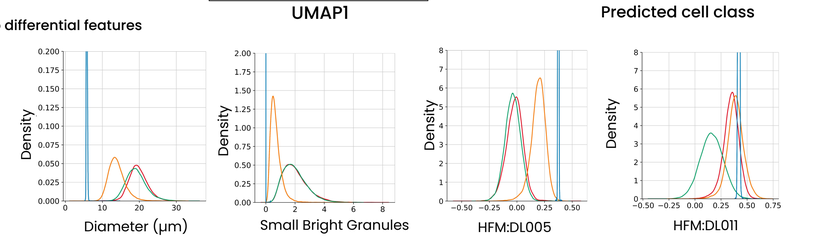

Figure 5. Evaluation of mixed cell types. 6μm polystyrene beads and three cancer cell lines w/ distinct features were imaged on the REM-I platform and combined *in silico* to evaluate HFM classification performance. **(A)** Table of cell classes, number of cell images analyzed, & representative images. **(B)** Morphology UMAP of 6μm beads and cancer cell lines colored by ground truth. **(C)** Confusion matrix: HFM predicts cell classes with high accuracy. **(D)** Density plots of top differential features by cell class. All cell lines have overlapping cell size distributions. A375 and Caov-3 are nearly identical in size, indicating that cell features other than size must be utilized to accurately differentiate A375 and Caov-3.

CONCLUSIONS

- Combining deep learning and morphometric features improves accuracy and interpretability.
- HFM characterizes and classifies synthetic cells and biological samples with high accuracy.
  - Features beyond cell size are utilized.
- The Deepcell Human Foundation Model (HFM) is fast and effective at extracting cell features, enabling real time cell classification and sorting.
- Real world applications of Deepcell's HFM on the REM-I platform include hypothesis-free sample exploration and adaptation to specific classification tasks.