

Uncovering host-virus interactions with imaging-based reverse genetics

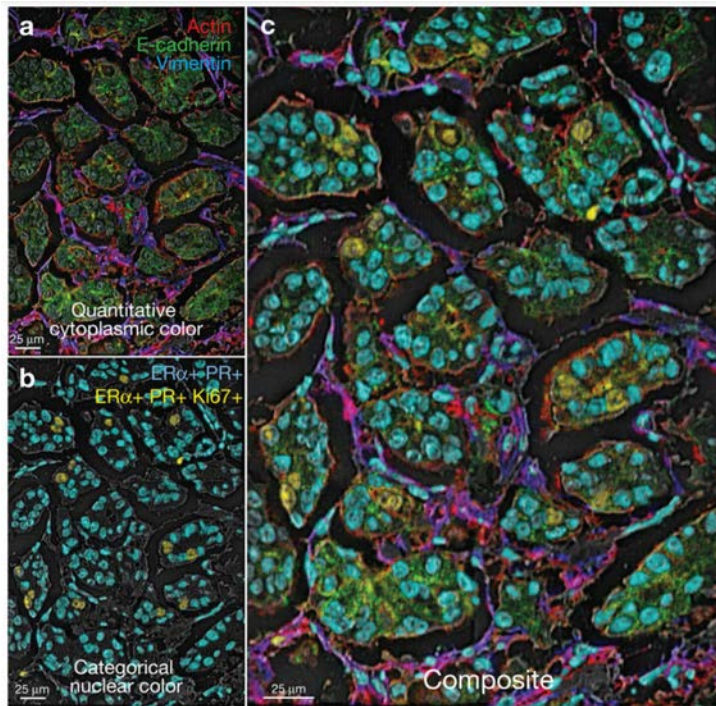
David Van Valen MD, PhD

NSF PREVENT

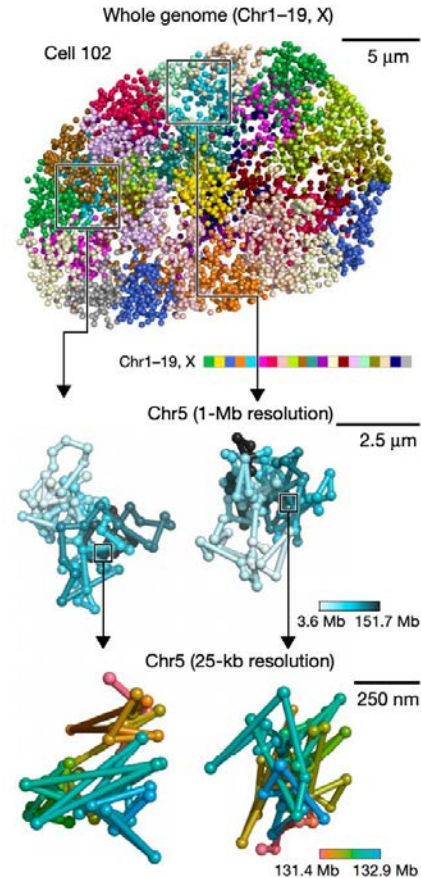
2/22/2021

Spatial genomics captures both the spatial and “parts list” variation of living matter in images

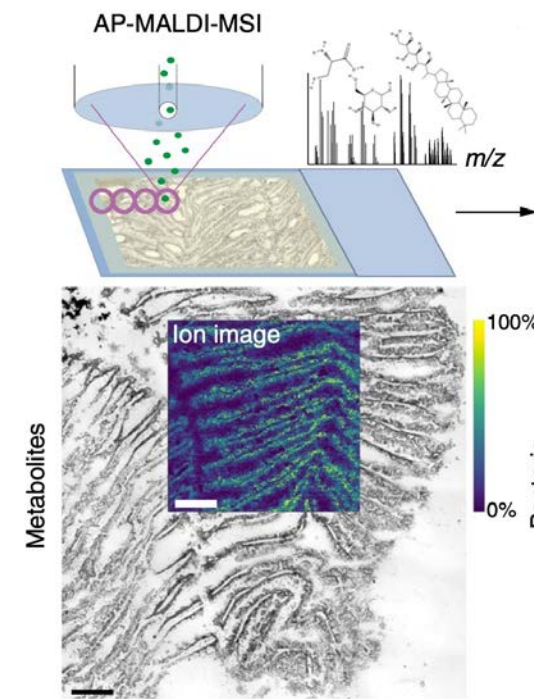
Spatial proteomics



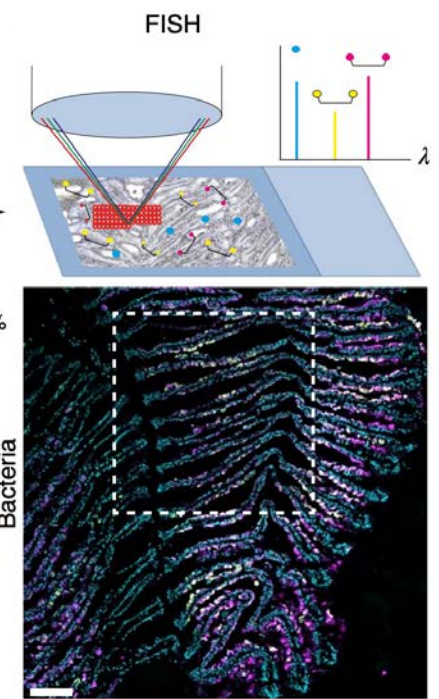
Spatial genomics



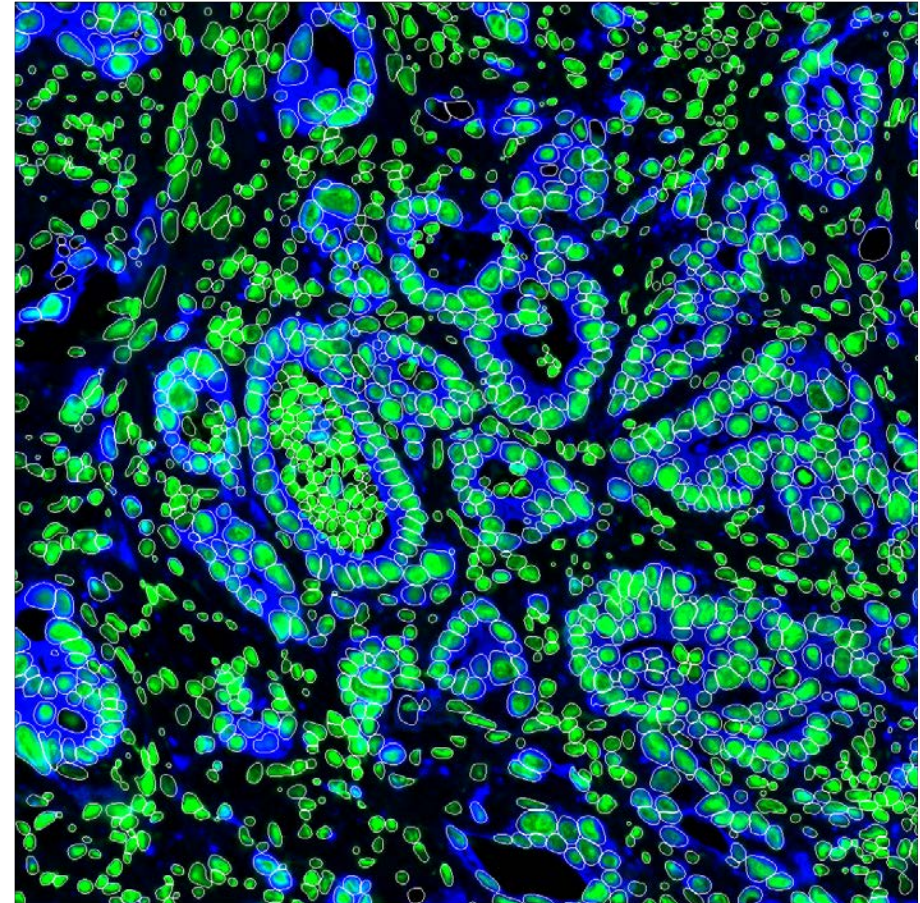
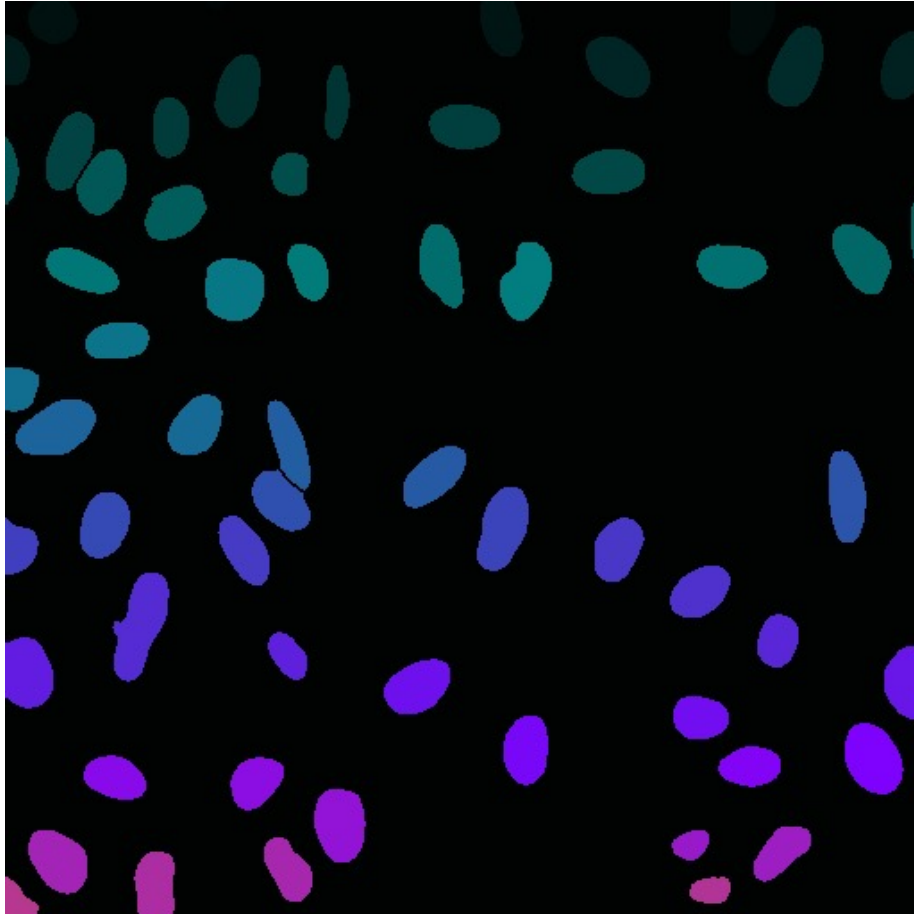
Spatial metabolomics



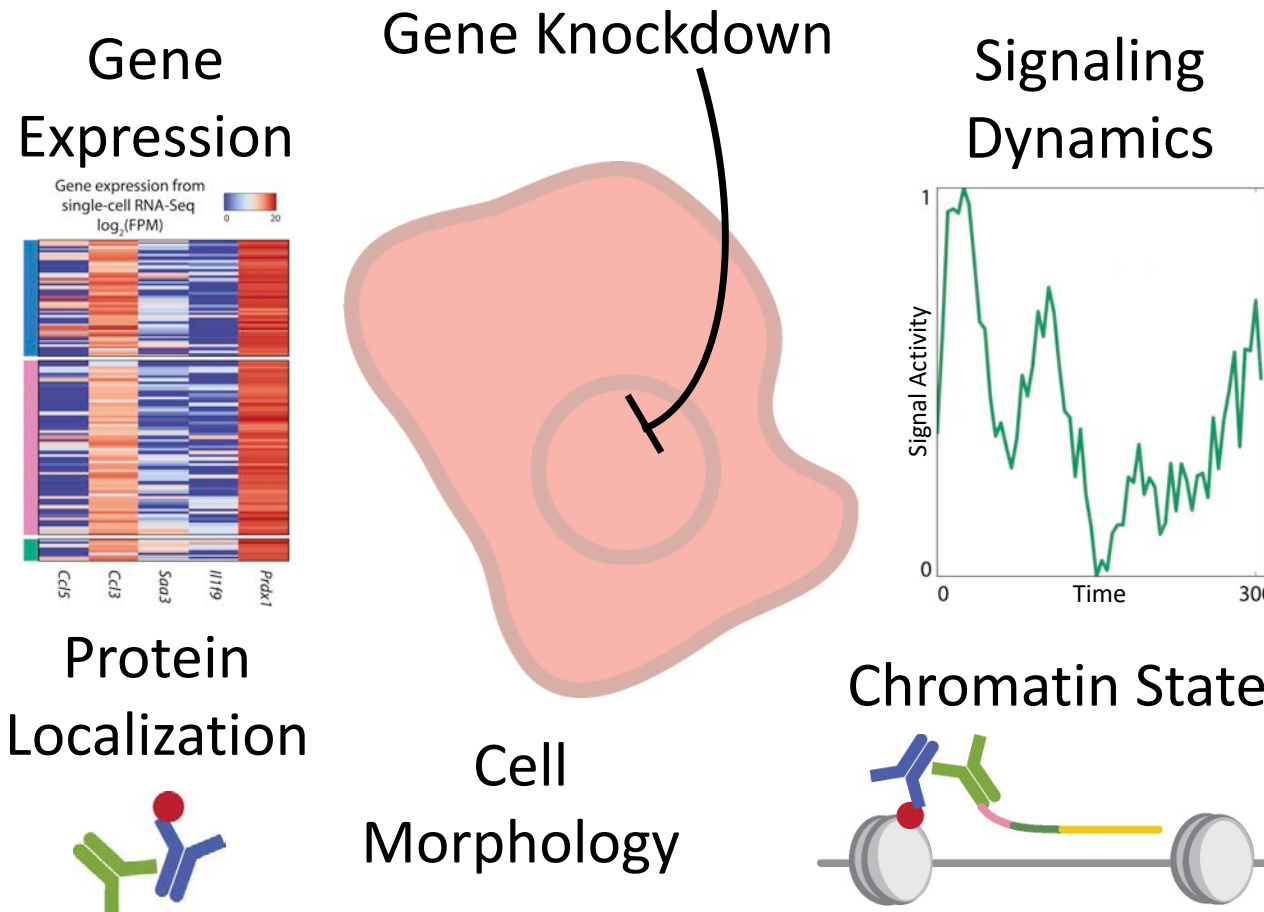
Spatial transcriptomics



Deep learning is changing how we interpret biological images

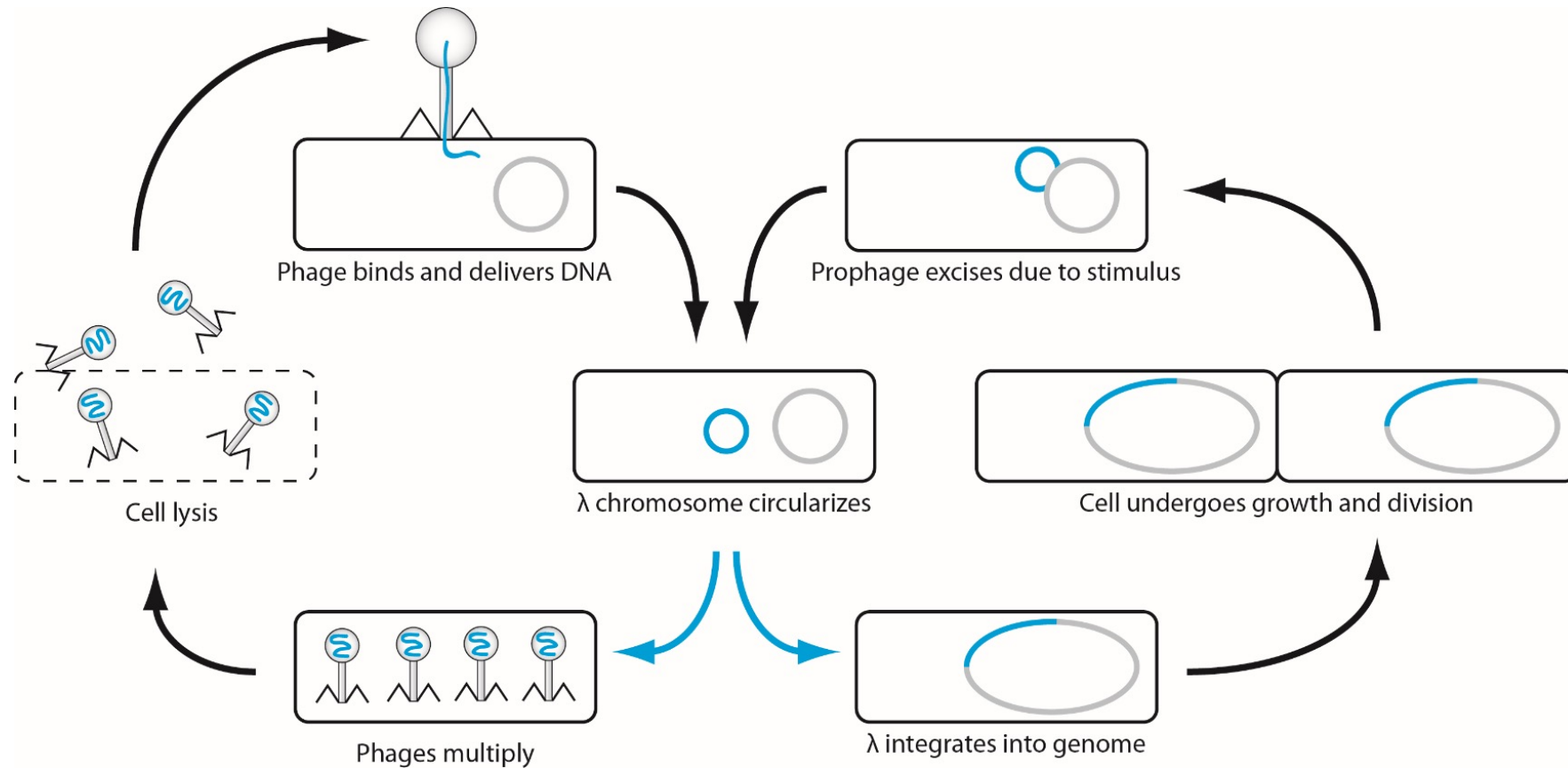


Deep learning and spatial genomics is a path to integrating heterogeneous measurements



As deep learning makes image analysis easier, biological data will increasingly be in the form of images

Host-virus interactions govern the viral life cycle



Imaging-based reverse genetics can reveal the role of the host in the viral lifecycle

Knockout library

Δ gene1

Δ gene2

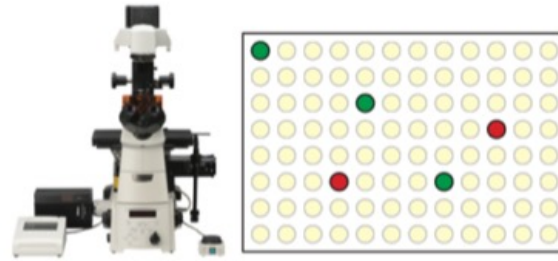
Δ gene3

Δ gene4

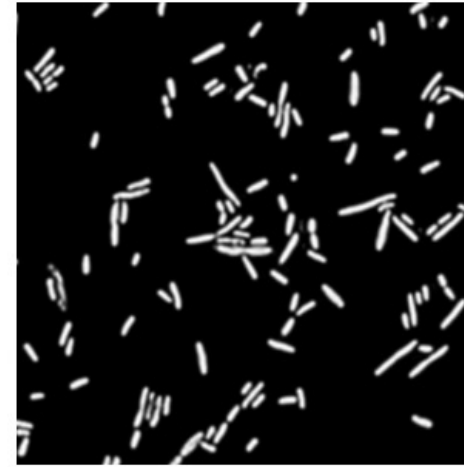
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Reporter virus

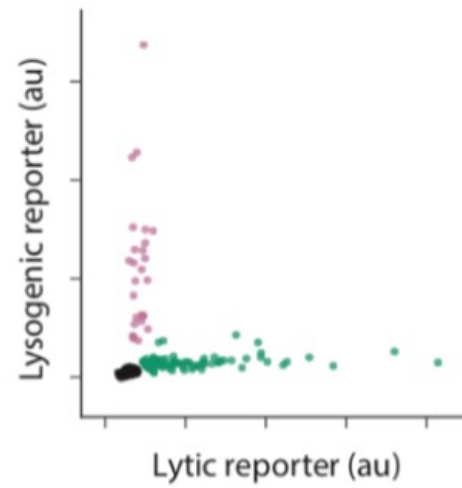




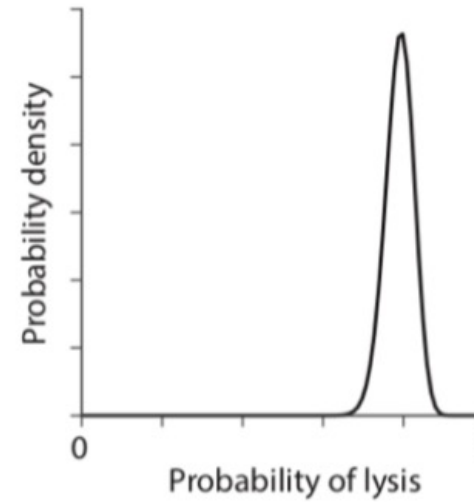
High-throughput imaging
of the infected Keio collection



Single-cell image segmentation
with deep learning

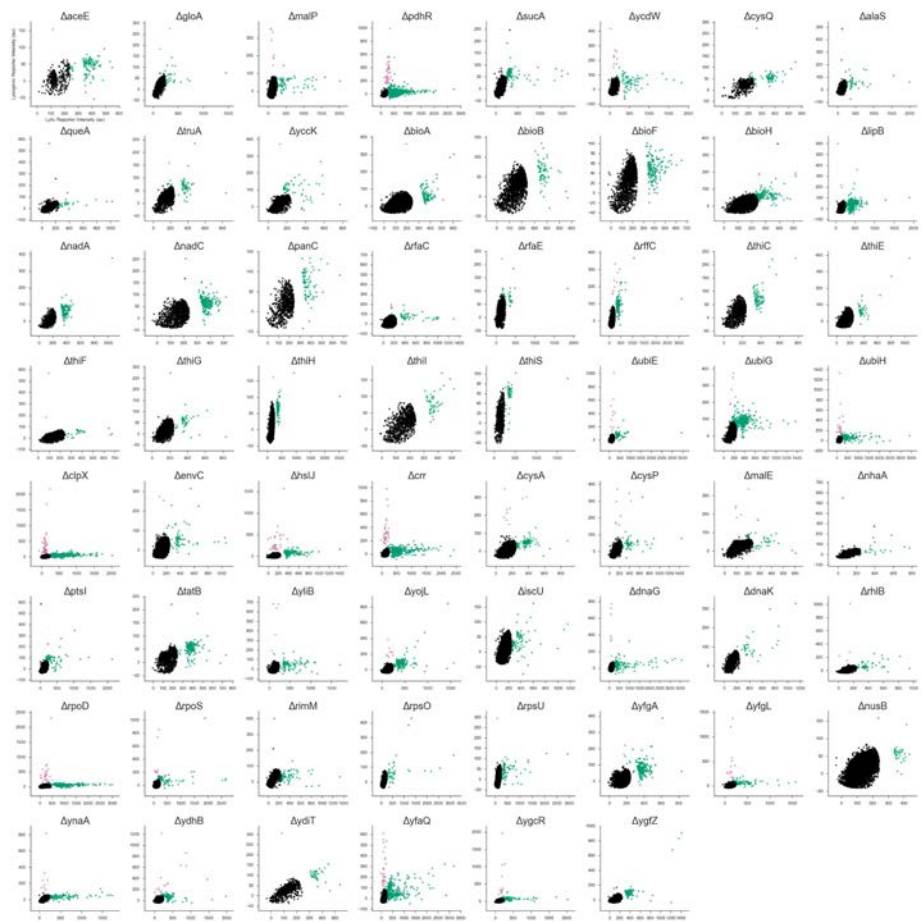


Fluorescence quantification
and infection classification

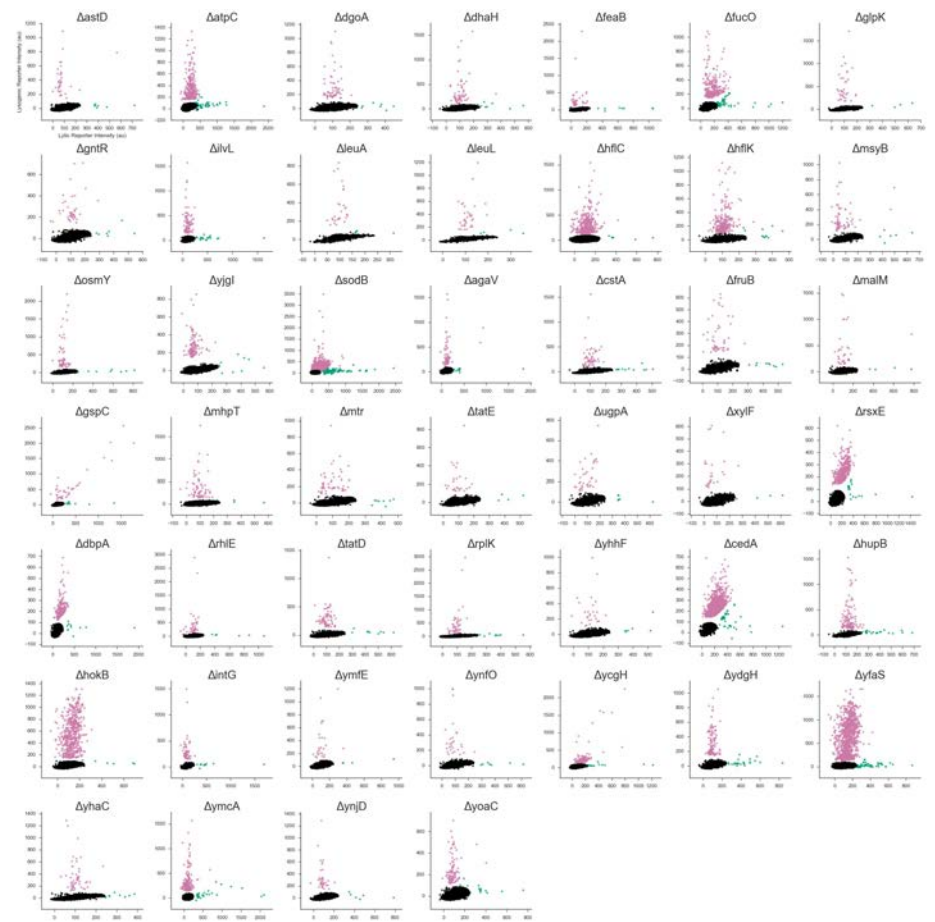


Bayesian inference to
quantify measurement
uncertainty

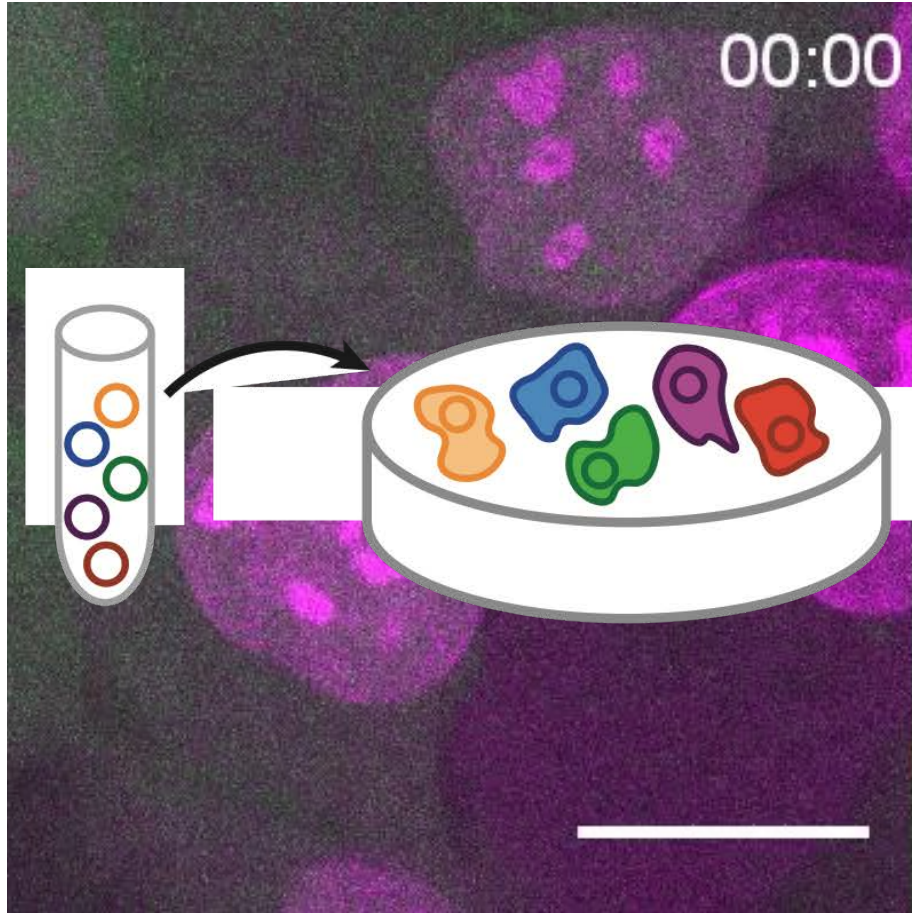
Active Hits



Latent Hits



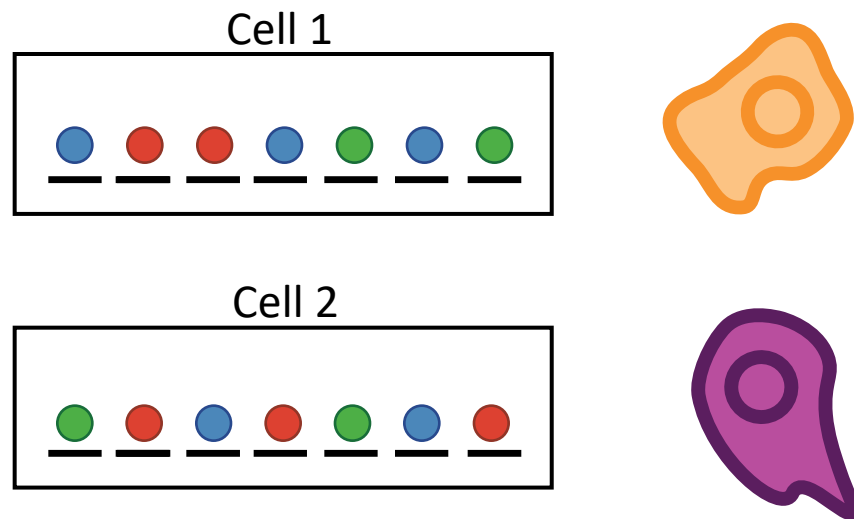
What about mammalian viruses?



- We can phenotype the life cycle of mammalian viruses with imaging
- Mammalian organisms have ~10 times more genes than bacteria
- CRISPR makes genome wide perturbation possible, but ...
 - Arrayed screens require laboratory automation
 - Pooled screens require a method to identify which cell received which guide RNA

Optical barcodes can link cells to their perturbation

Temporal Barcodes

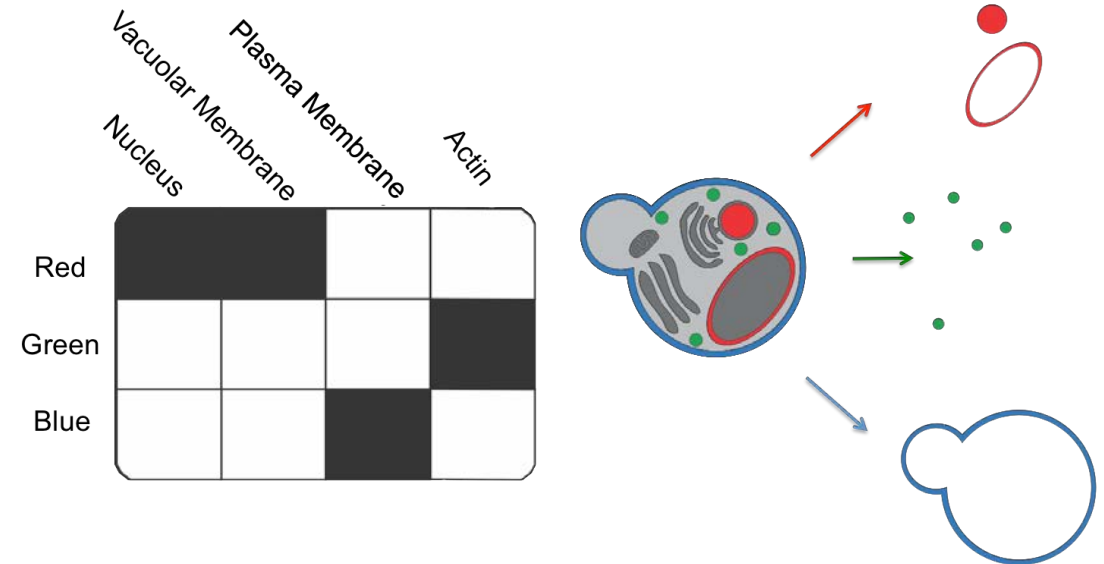


Fluorescent *In Situ* Hybridization

14 rounds

40 hours

Spatial Barcodes



	Vacuolar Membrane	Plasma Membrane	Actin
Red	Black	White	White
Green	White	White	Black
Blue	White	White	Black

$\sim 2^{\text{Color} \times \text{Compartments}}$

3 compartments

4 colors

4096 genes

or

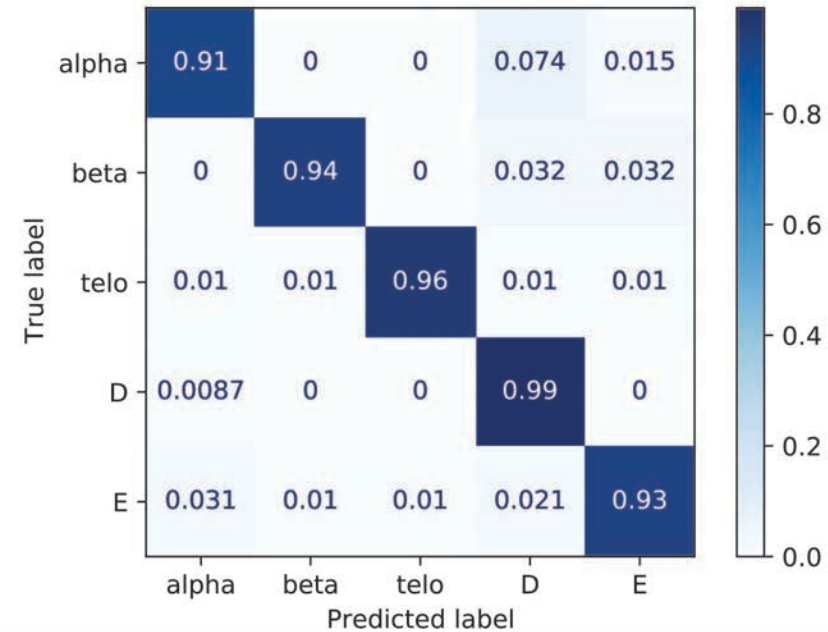
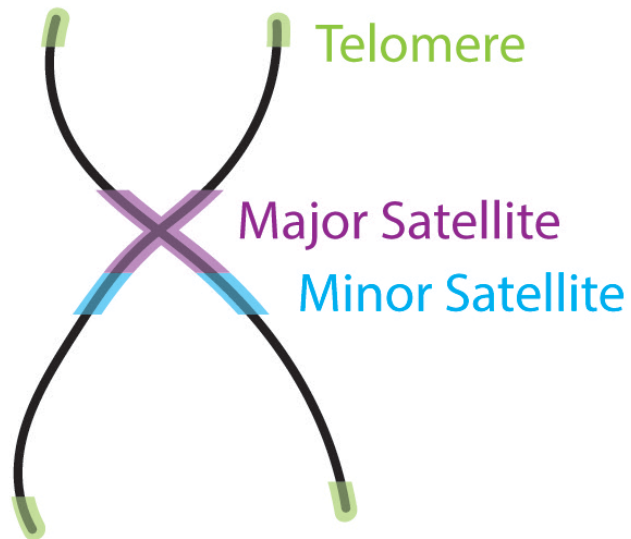
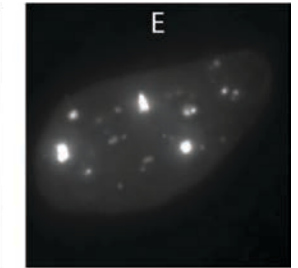
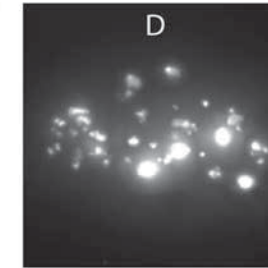
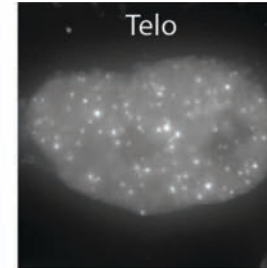
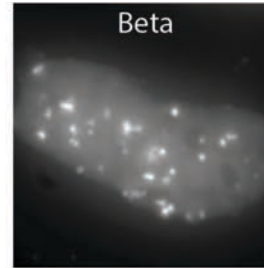
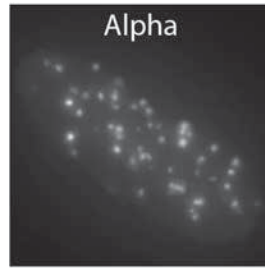
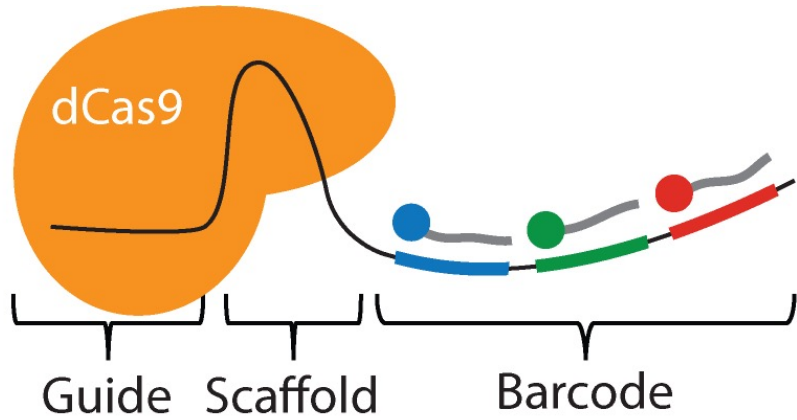
$\sim \text{Compartments}^{\text{Color}}$

10 compartments

4 colors

10,000 genes

Generating optical barcodes with CRISPR-Display and RNA FISH



Thanks!

The Van Valen Lab

Will Graf

Edward Pao

Tom Dougherty

Geneva Miller

Erick Moen

Uriah Israel

Emily Laubscher

Morgan Schwartz

Dylan Bannon

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Noah Greenwald

Michael Angelo

The Keren Lab

Leeat Keren

The Cai Lab

Long Cai

Noushin Koulena

Nico Pierson

The Yue Lab

Uriah Israel

Cloud Posse

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