Isolating the perturbation response of gene regulatory networks in the presence of biological variability and technical noise

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Drug-induced reprogramming as a mode of cancer drug resistance

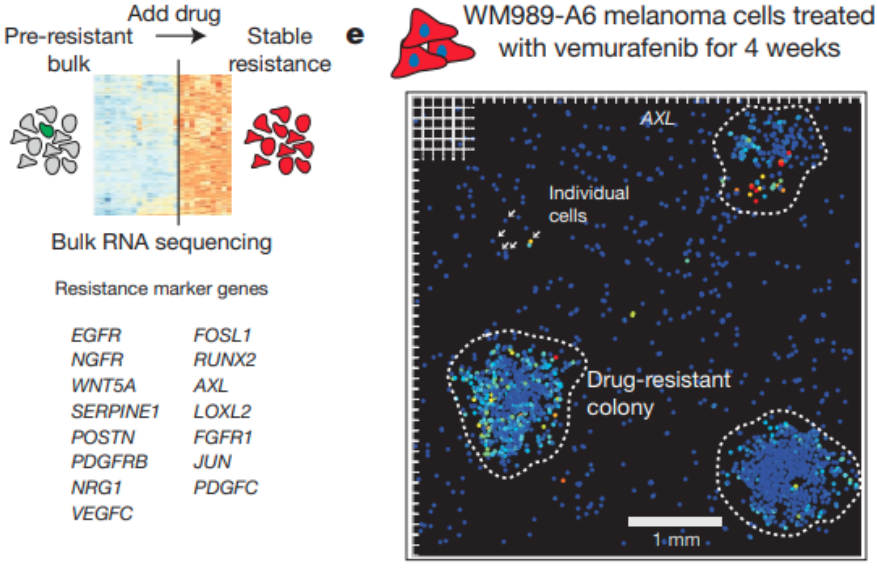
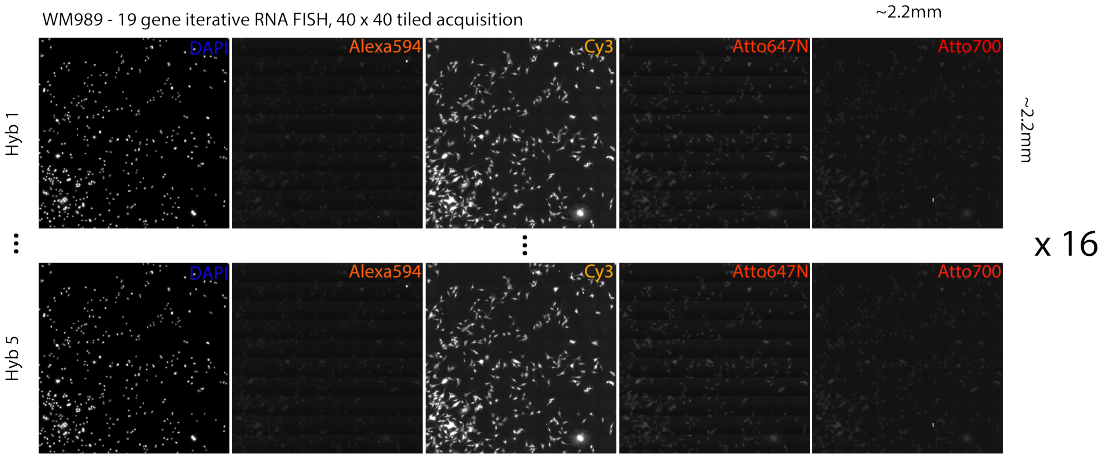


Figure 1: Shaffer et al., Nature 2017

WM989-A6 RNA-FISH data summary



Graphical abstract

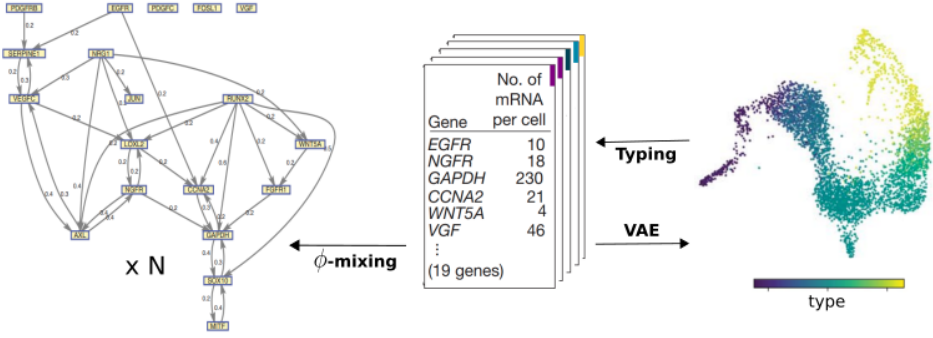


Figure 2: *Gene expression matrices used as training data to learn a latent-space representation of gene expression, uncovering latent structure of the joint distribution and permitting cell typing, account for batch variability. Type information is then used for inference of the underlying regulatory network using the phi-mixing coefficient, which may differ across types*

Simulating gene expression *in-silico*

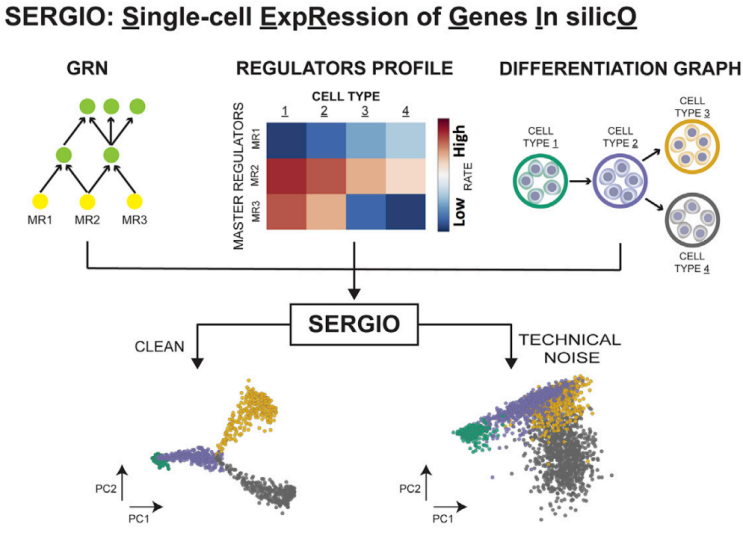


Figure 3: (Dibaeinia and Sinha, Cell Systems 2020)

Simulating gene expression *in-silico*

We can simulate the expression of a gene as a function of the levels of its regulators (TFs), as prescribed by a fixed gene regulatory network (GRN)

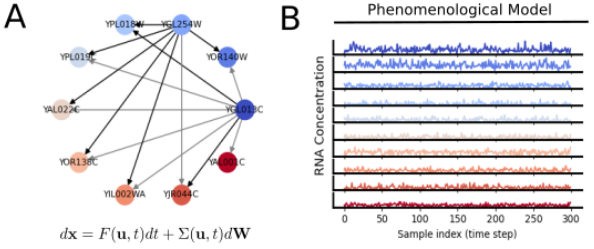
This is done via the chemical Langevin equation (Gillespie, 2000; Dibaeinia 2020):

$$\dot{x}_i = P_i(t) - \lambda_i x_i(t) + q_i \left(\sqrt{P_i(t)}\alpha + \sqrt{\lambda_i x_i}\beta \right)$$

The transcription rate of gene i depends non-linearly on its regulators:

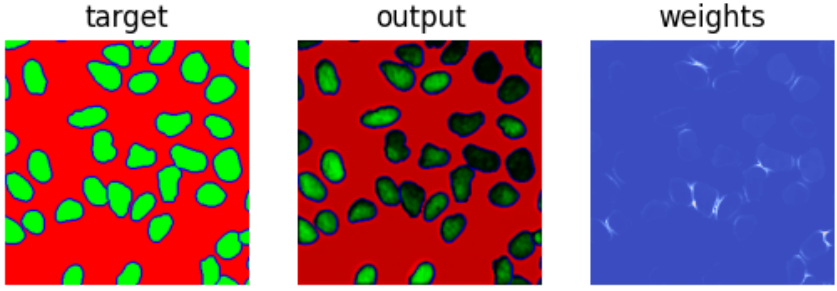
$$P_i = \sum_j p_{ij} + b_i$$

$$p_{ij} = m_{ij} \frac{x_{ij}^{n_{ij}}}{x_{ij}^{n_{ij}} + h_{ij}^{n_{ij}}}$$



Training on BBBC039 U2OS Cells

BBBC039: 200 images, 160 train + 40 validation, 256 x 256 random crop

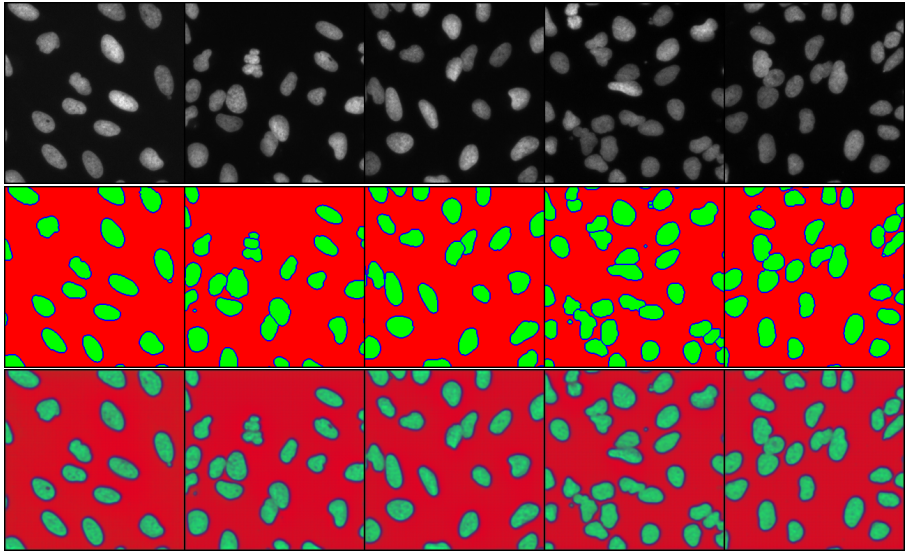


We train a 3-channel semantic segmentation model with **weighted** cross-entropy loss:

$$\mathcal{L} = \sum_{i,j} w_{ij} \log p_{ij}(\tilde{x}) = \sum_{i,j} w_{ij} \log \frac{\exp(-s_{ij}(\tilde{x}))}{\sum_{x \in \chi} \exp(-s_{ij}(\tilde{x}))}$$

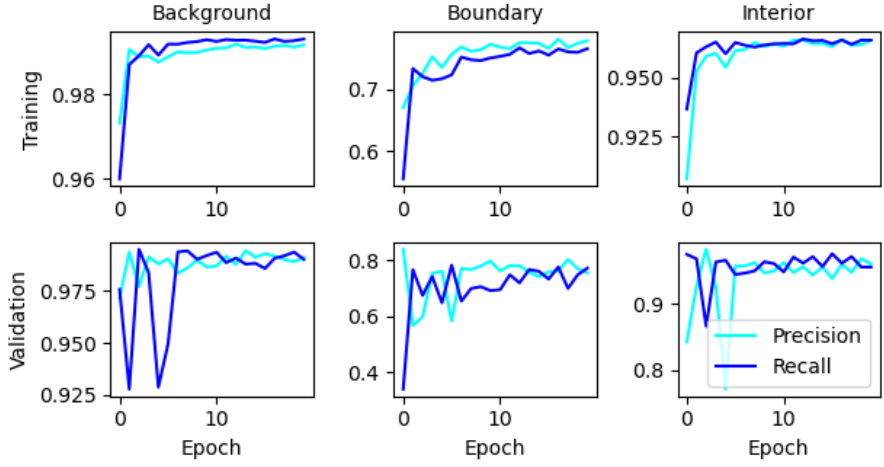
p_{ij} is the probability the model assigns a pixel to the true class $\tilde{x} \in \{\mathrm{a}, \mathrm{b}, \mathrm{c}\}$

Training on BBBC039 U2OS Cells



Training on BBBC039 U2OS Cells

Learning rate $\eta = 0.01$, Batch-size $B = 5$ (32 train iterations, 8 validation)



References I