CELL DETECTION ON IMAGE-BASED IMMUNOASSAYS

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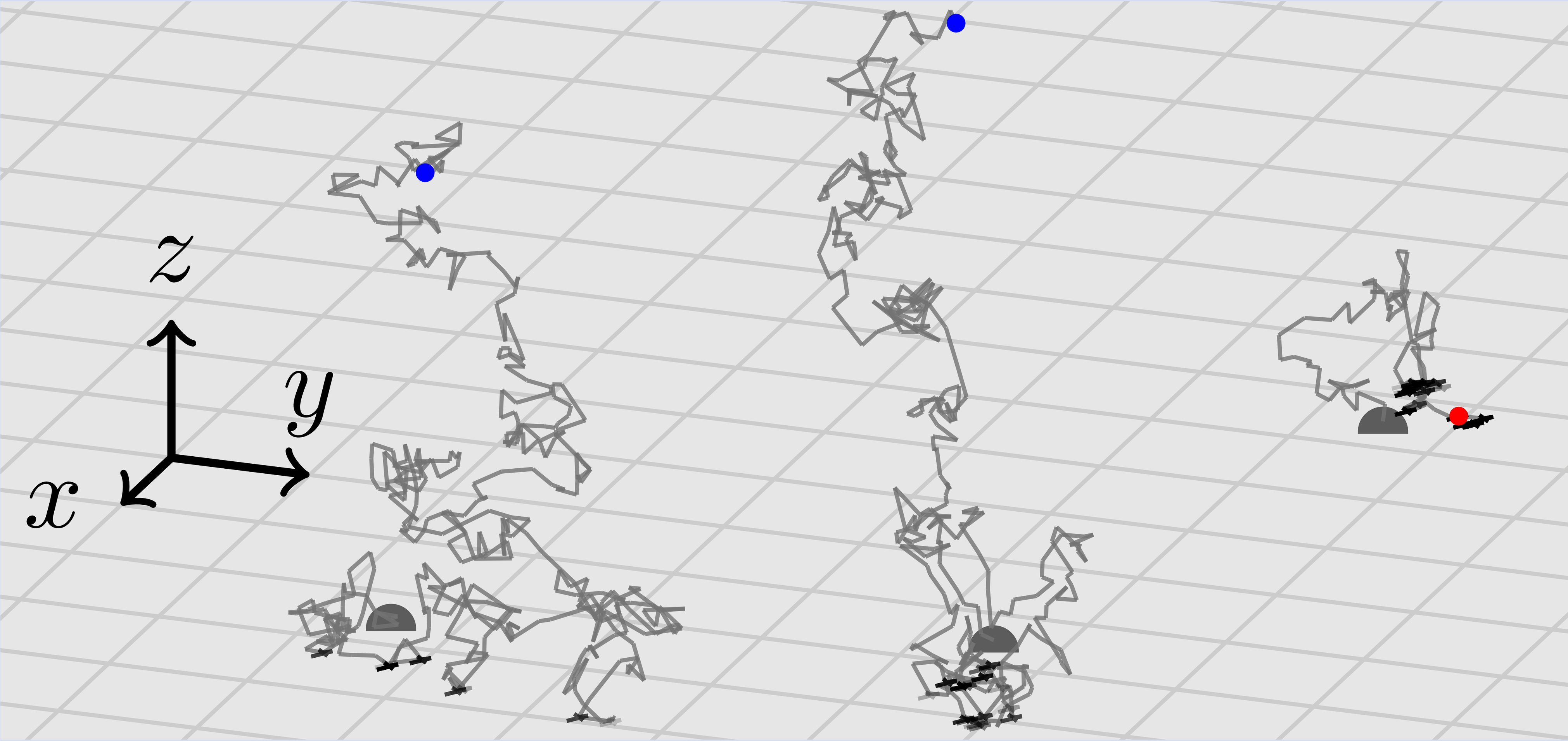
Physical model for Fluorospot and Elispot



- Cells (dark gray) generate particles
- Particles move in a Brownian motion
- If they hit $z = 0$, they may be adsorped (black marks)
- They may later desorb and be free at time T (blue dots, not imaged)
- They may be bound at time T and imaged (red dot)
- We want to recover the location of the cells

An image measures the density of bound particles $d(x, y, t)$ at time T, that depends on the 3D density of free particles $c(x, y, z, t)$ and the source density rate of new particles $s(x, y, t)$ according to

$$\frac{\partial}{\partial t} d = \kappa_{\mathrm{a}} c\big|_{z=0} - \kappa_{\mathrm{d}} d\,,$$

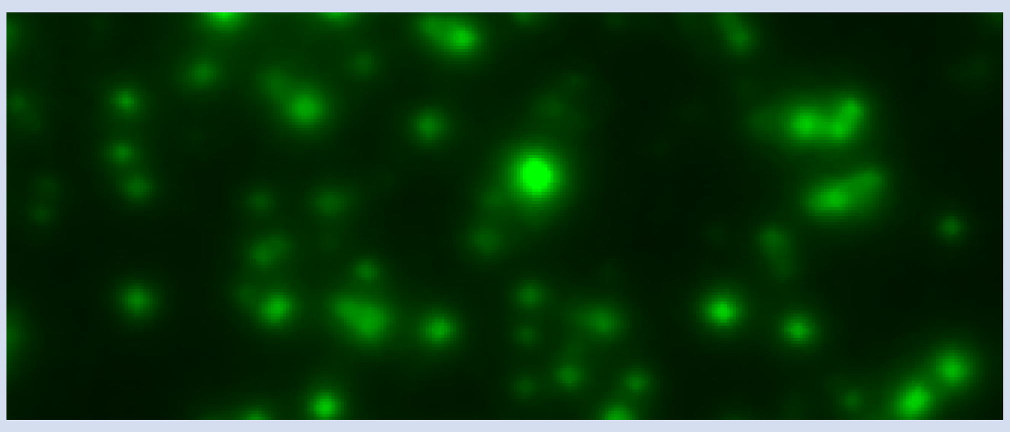
$$\underbrace{\frac{\partial}{\partial t} c = D\Delta c\,,}_{\textit{diffusion}} \quad \underbrace{-D\frac{\partial}{\partial z} c\big|_{z=0} = s + \kappa_{\mathrm{d}} d - \kappa_{\mathrm{a}} c\big|_{z=0}\,.}_{\textit{reaction-adsorption-desorption}}$$

Observation model for Fluorospot and Elispot

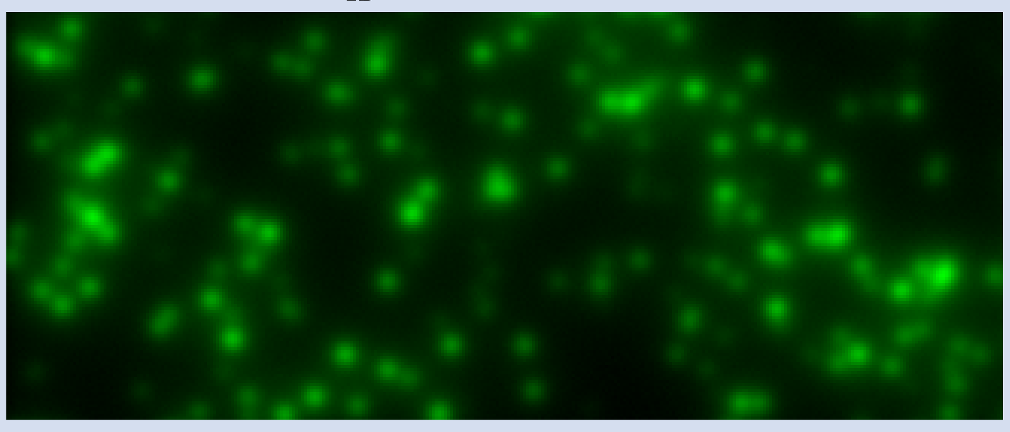
- Independence of Brownian motion the three spatial dimensions
- Adsorption and desorption only disrupt z-movement
- x- and y-movements only depend on the total time spent on Brownian motion, and can be characterized through the Green function $g_{\sqrt{2D\tau}}(x, y)$
- Characterize the distribution $\varphi(\tau, t)$ of spending τ seconds in free motion and being bound at time t
- Change variables, $\sigma = \sqrt{2D\tau}$

Then, the image observation $d_{\mathrm{obs}}(x, y)$ can be expressed as

$$d_{\mathrm{obs}}(x, y) = \int_0^{\sigma_{\max}} g_\sigma(x, y) * a(x, y, \sigma)\mathrm{d}\sigma, \text{ with } a(x, y, \sigma) = \frac{\sigma}{D}\int_{\frac{\sigma^2}{2D}}^{T} s(x, y, T-\eta)\,\varphi\left(\frac{\sigma^2}{2D}, \eta\right)\mathrm{d}\eta.$$



Real observation (section)



Simulated observation (section)

Inverse problem for cell detection

We propose to invert a discrete approximation of the observation model by solving the weighted least-squares, non-negative group-sparsity regularized optimization problem

$$\min_{\tilde{a} \in \mathbb{R}_+^{M\times N\times K}} \left\{ \left\| \tilde{d}_{\mathrm{obs}} - \sum_{k=1}^{K} \tilde{g}_k \circledast \tilde{a}_k \right\|_{\tilde{w}}^2 + \lambda \sum_{m,n} \|\tilde{a}_{m,n}\|_2 \right\}$$

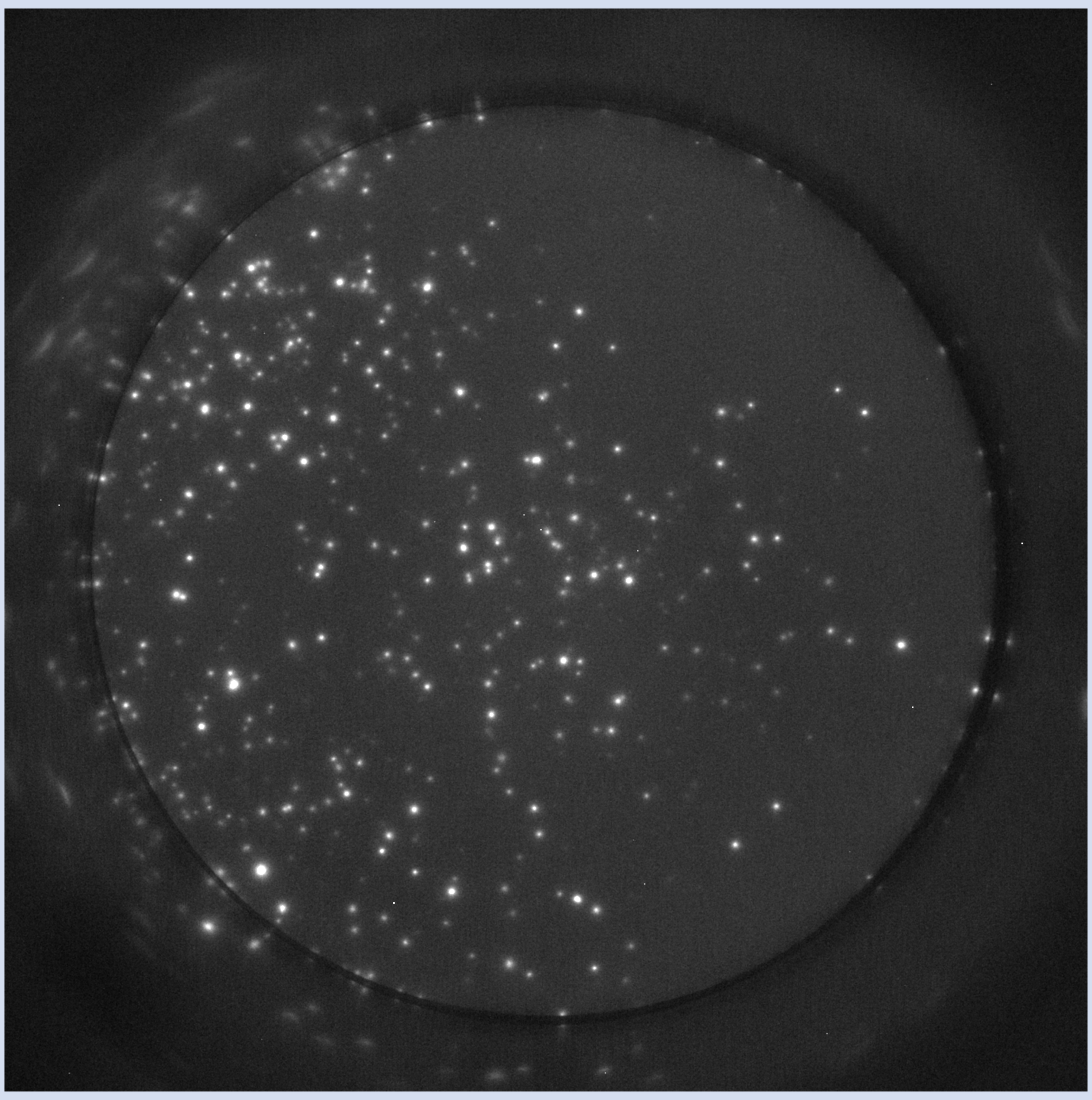
where $\tilde{a}_k \in \mathbb{R}_+^{M\times N}$ and $\tilde{a}_{m,n} \in \mathbb{R}_+^{K}$. Here, the k-grouping couples the representations of each location across different scales or times, while the spatial sparsity favors accurate localization.

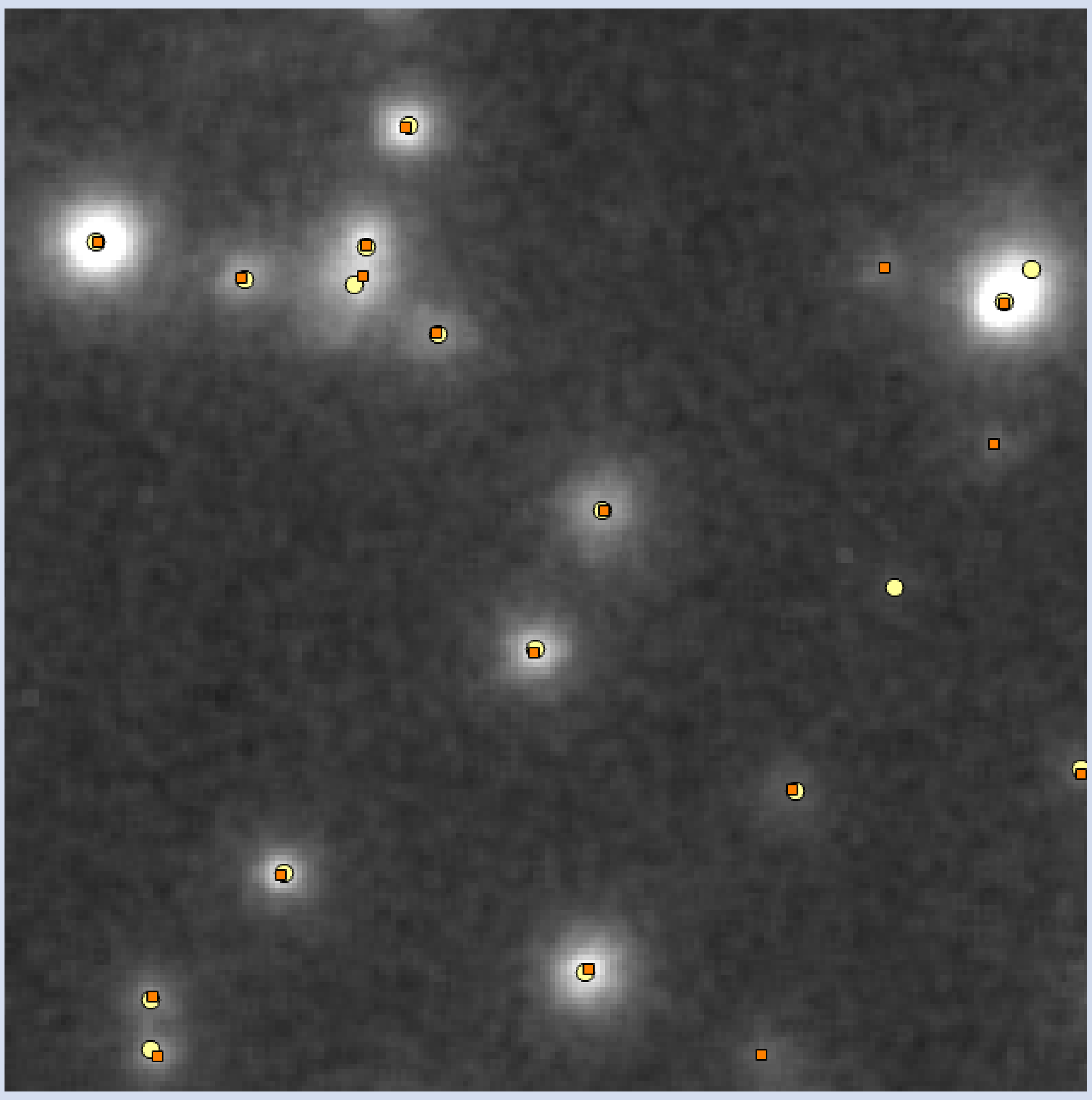
Algorithm

Require: An initial $\tilde{a}^{(0)} \in \mathbb{R}_+^{M\times N\times K}$, a discrete image observation $\tilde{d}_{\mathrm{obs}} \in \mathbb{R}_+^{M\times N}$

1: $\tilde{b}^{(0)} \leftarrow \tilde{a}^{(0)}$, $i \leftarrow 0$
2: **repeat**
3: $\quad i \leftarrow i + 1$
4: $\quad \tilde{d}^{(i)} \leftarrow \sum_{k=1}^{K} \tilde{g}_k \circledast \tilde{b}_k^{(i-1)} - \tilde{d}_{\mathrm{obs}}$
5: $\quad$ **for** $k = 1$ **to** K **do**
6: $\quad\quad \tilde{a}_k^{(i)} \leftarrow \left[\tilde{b}_k^{(i-1)} - \eta\tilde{g}_k \circledast \left[\tilde{w}^2 \odot \tilde{d}^{(i)}\right]\right]_+$
7: $\quad$ **end for**
8: $\quad \tilde{p} \leftarrow \left(1 - \frac{\eta}{2}\lambda\left[\sqrt{\sum_{k=1}^{K}\left(\tilde{a}_k^{(i)}\right)^2}\right]^{-1}\right)_+$
9: $\quad$ **for** $k = 1$ **to** K **do**
10: $\quad\quad \tilde{a}_k^{(i)} \leftarrow \tilde{p} \odot \tilde{a}_k^{(i)}$
11: $\quad$ **end for**
12: $\quad \tilde{b}^{(i)} \leftarrow \tilde{a}^{(i)} + \alpha(i)\left(\tilde{a}^{(i)} - \tilde{a}^{(i-1)}\right)$
13: **until** convergence
14: $\tilde{a}_{\mathrm{opt}} \leftarrow \tilde{a}^{(i)}$

Accelerated proximal gradient algorithm to obtain $\tilde{a}$. Lines 4 and 6 optimize the least squares term, while Lines 8 and 10 optimize the regularizer. The $\alpha(i)$s control the Nesterov acceleration, $\eta = \tilde{\sigma}_{\max}^{-1}/\max|\tilde{w}_{m,n}|^2$ is the algorithm's fixed step size, $\circledast$ is the discrete convolution, and matrix products ($\odot$) and powers are element-wise.





To the left, grayscale image data, with increased luminosity to ease visualization. To the right, cell detection results (yellow circles) and human expert labeling (orange squares) on a section of the image, superposed to the grayscale image data. The resulting detection performance, with respect to the expert human labeler and with a tolerance of 3 pix, was and **F1-Score** of **0.9** with precision 0.92 and recall 0.88.