Cell Detection by Functional Inverse Diffusion and Group Sparsity

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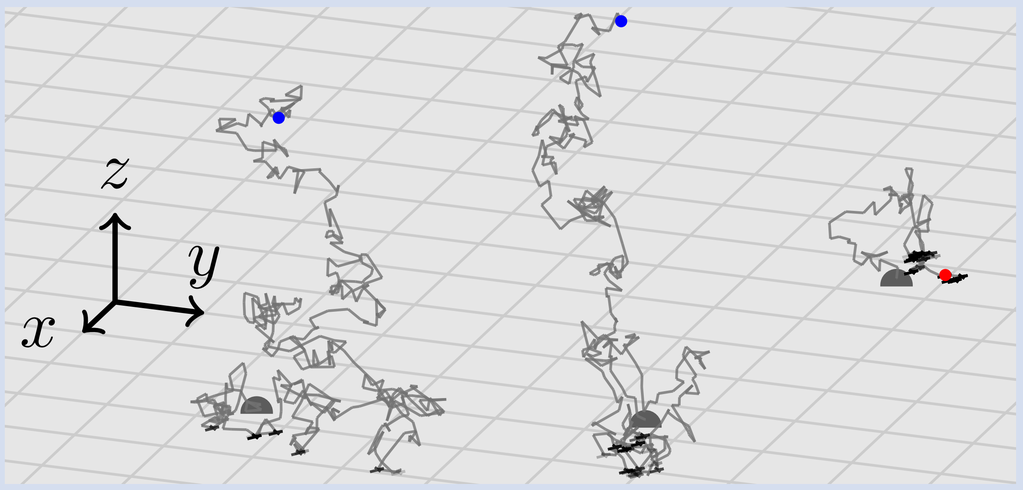
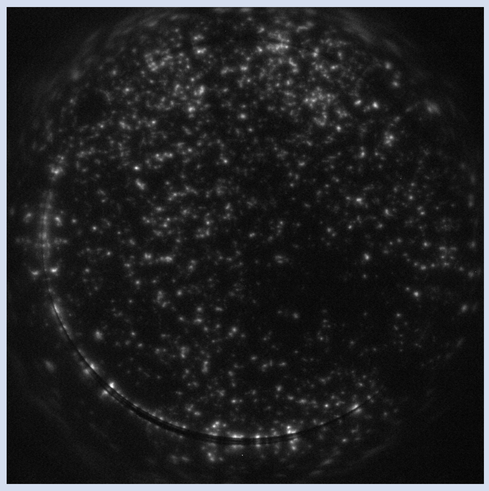
A Physical Model for Biomedical Assays





- Active cells (dark gray) generate particles
- Particles move in a Brownian motion (through $z > 0$)
- If they hit the plane, they might bind (adsorption, black marks)
- They might later escape (desorption) and be free at time T (blue dots, not captured, not observed)
- They may be bound at time T and appear in the image (red dot)
- One wants to recover the location of the active cells

The image measures the spatial density of bound particles $d : \mathbb{R}^2 \times \mathbb{R}_+ \to \mathbb{R}_+$ at time T. This quantity evolves in time coupled to the 3D density of free particles $c : \mathbb{R}^2 \times \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$ and the source density rate of new particles generated at each time and location on the plane $s : \mathbb{R}^2 \times \mathbb{R}_+ \to \mathbb{R}_+$, according to the partial differential equations

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

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

diffusion *reaction-adsorption-desorption*

An Observation Model

- Consider independence of Brownian motion in the different dimensions
- Observe that adsorption and desorption only disrupt z-movement
- Conclude that x- and y-movements will only depend on the total time spent on Brownian motion, and that these will be characterized according to the Green function of the homogeneous diffusion equation in 2D, $g_{\sqrt{2D\tau}}(x, y)$
- Summarize the effect of adsorption and desorption by obtaining $\varphi(\tau, t)$, based on the time-density of spending τ seconds in free motion before the first binding event, $\phi(\tau)$
- Change variables, from total time in Brownian motion τ, to the displacement it causes $\sigma = \sqrt{2D\tau}$

We consider the image observation $d_{\mathrm{obs}} = d(x, y, T) \in \mathcal{D}_+ = \left(\mathrm{L}^2_+\left(\mathbb{R}^2\right), (w\,\cdot, w\,\cdot)\right)$ for some bounded weighting function $w(x, y)$ and prove that

$$d_{\mathrm{obs}}(x, y) = \int_0^{\sigma_{\max}} G_\sigma\, a(x, y, \sigma)\mathrm{d}\sigma = Aa\,, \qquad (1)$$

with $a \in \mathcal{A}_+ = \left(\mathrm{L}^2_+\left(\mathbb{R}^2 \times \mathbb{R}_+\right), (\mu\,\cdot, \mu\,\cdot)\right)$ for some 2D $(0, 1)$-masking function $\mu(x, y)$, $A : \mathcal{A} \to \mathcal{D}$, and

$$a(x, y, \sigma) = \frac{\sigma}{D} \int_{\frac{\sigma^2}{2D}}^{T} s(x, y, T - \eta)\, \varphi\left(\frac{\sigma^2}{2D}, \eta\right) \mathrm{d}\eta, \text{ with}$$

$$\varphi(\tau, t) = i_{[0,t)}(\tau) \sum_{j=1}^{\infty} \phi^{j*}(\tau) p\left[j - 1; \kappa_{\mathrm{d}}(t - \tau)\right]\,,$$

where $p[j, \lambda]$ is the Poisson PMF, and $\phi^{j*}(\tau)$ the j-th convolutional power of

$$\phi(\tau) = \frac{\kappa_{\mathrm{a}}}{\sqrt{\pi D\tau}} - \frac{\kappa_{\mathrm{a}}^2}{D} \mathrm{erfcx}\left(\kappa_{\mathrm{a}}\sqrt{\frac{\tau}{D}}\right)\,.$$

An Inverse Problem, Functional Inverse Diffusion (FID)

- Pose a convex inverse problem with group-sparsity regularization that can be solved by the Accelerated Proximal Gradient (APG) algorithm

$$\min_{a \in \mathcal{A}_+} \left[\|Aa - d_{\mathrm{obs}}\|^2_{\mathcal{D}} + \lambda \left\| \|\xi a_{\mathbf{r}}\|_{\mathrm{L}^2[0,\sigma_{\max}]} \right\|_{\mathrm{L}^1(\mathbb{R}^2)} \right]\,. \qquad (2)$$

- Characterize the diffusion operator A in terms of

  i) a bound on its operator norm, using that $w(x, y)$ is bounded, Jensen's inequality and the unit norm of the Gaussian blur operator,

  $$\|A\|_{\mathcal{L}(\mathcal{A},\mathcal{D})} \leq \sqrt{\sigma_{\max}}\, \|w\|_{\mathrm{L}^\infty(\mathbb{R}^2)}\,,$$

  ii) its adjoint operator, using that the Gaussian blur operator is self-adjoint,

  $$\left(A^* d\right)(x, y, \sigma) = \mu(x, y) G_\sigma\{w^2(x, y) d(x, y)\}\,.$$

- Deriving the proximal operator of the non-negatively-constrained group-sparsity regularizer in (2), by adding the non-negativity constraint to the usual path for the prox of a norm, i.e., Fenchel conjugate, projection on the dual ball (ellipsoid) and Moreau's decomposition. For the specific case of $\xi(\sigma)$ a $(0, 1)$-indicator of the set $\aleph \subset [0, \sigma_{\max}]$, we have that, if $p = \mathrm{prox}_{\gamma\mathcal{R}}(a)$, and we decompose $a(x, y, \sigma) = a_\aleph(x, y, \sigma) + a_{\aleph^{\mathrm{c}}}(x, y, \sigma)$,

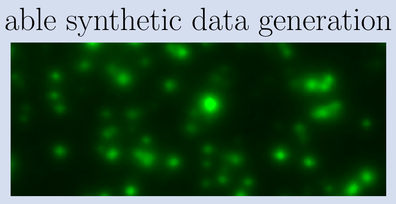
$$p(x, y, \sigma) = \left[a_{\aleph^{\mathrm{c}}}(x, y)\right]_+ + \left[a_\aleph(x, y)\right]_+ \left(1 - \frac{\gamma\lambda}{\left\|\left[a_\aleph\right]_+\right\|_{\mathrm{L}^2(\aleph)}}\right)_+\,.$$

Biological Context

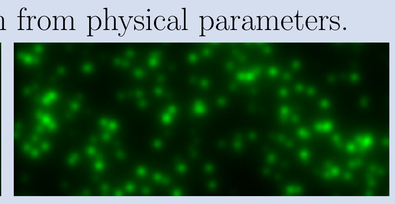
Fluorospot and ELISPOT biomedical assays, among others, follow this physical model. These are widely used in pharmacological development, medical research (e.g., immunology), and diagnosis of diseases (e.g., tuberculosis).

Results, Diffusion Operator A

Our novel observation model (1) enables, among others, reliable synthetic data generation from physical parameters.



Real observation (section)



Simulated observation (section)

FID Algorithm

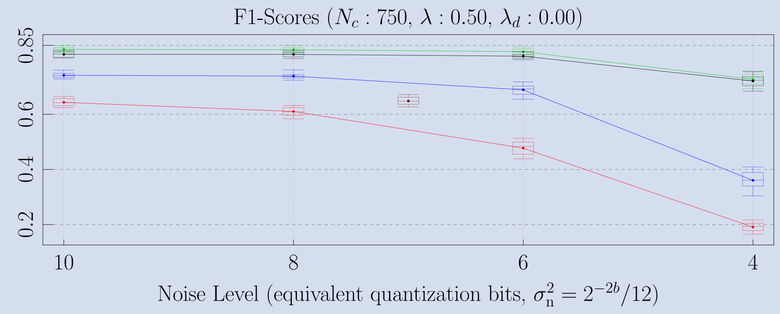
Require: Initial $a^{(0)} \in \mathcal{A}_+$, image observation $d_{\mathrm{obs}} \in \mathcal{D}_+$
Ensure: A solution $a_{\mathrm{opt}} \in \mathcal{A}_+$ that solves (2)

1: $b^{(0)} \leftarrow a^{(0)}$, $i \leftarrow 0$
2: **repeat**
3: $\quad i \leftarrow i + 1$, $\alpha \leftarrow \frac{t(i-1)-1}{t(i)}$
4: $\quad a^{(i)} \leftarrow \left[b^{(i-1)} - \eta A^*\left(Ab^{(i-1)} - d_{\mathrm{obs}}\right)\right]_+$
5: $\quad a^{(i)}_\aleph \leftarrow a^{(i)}_\aleph \left(1 - \frac{\eta}{2}\lambda \left\|a^{(i)}_{\mathbf{r},\aleph}\right\|^{-1}_{\mathrm{L}^2(\aleph)}\right)_+$
6: $\quad b^{(i)} \leftarrow a^{(i)} + \alpha\left(a^{(i)} - a^{(i-1)}\right)$
7: **until** convergence
8: $a_{\mathrm{opt}} \leftarrow a^{(i)}$

APG algorithm (also known as FISTA) to find a_{opt} that solves (2) with cost functional value convergence rate $\mathcal{O}\left(i^{-2}\right)$. Case $\xi = i_\aleph(\sigma)$ with $\aleph \subset [0, \sigma_{\max}]$. Here, $\eta = \sigma^{-1}_{\max} \|w\|^{-2}_{\mathrm{L}^\infty(\mathbb{R}^2)}$ is used for clarity of exposition.

Results, Cell Detection

$$\mathrm{pre} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FP}},\ \mathrm{rec} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}},\ \text{and } \mathrm{F1} = \frac{2\,\mathrm{pre} \cdot \mathrm{rec}}{\mathrm{pre} + \mathrm{rec}}$$



Detection by max-picking and optimal thresholding. In green and black, best rank 3 and rank 1 approximations to kernels using the algorithm above, respectively. In blue, deconvolution using algorithm above and best blur kernel possible. In dark-red and red, directly on image, without any noise and with noise, respectively.

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