Cell detection by functional inverse diffusion and group sparsity

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Joint work with: Joakim Jaldén

Funds to ACK: Mabtech AB, VR, KTH Opportunities Fund, and Knut and Alice Wallenberg Foundation

KTH Royal Institute of Technology

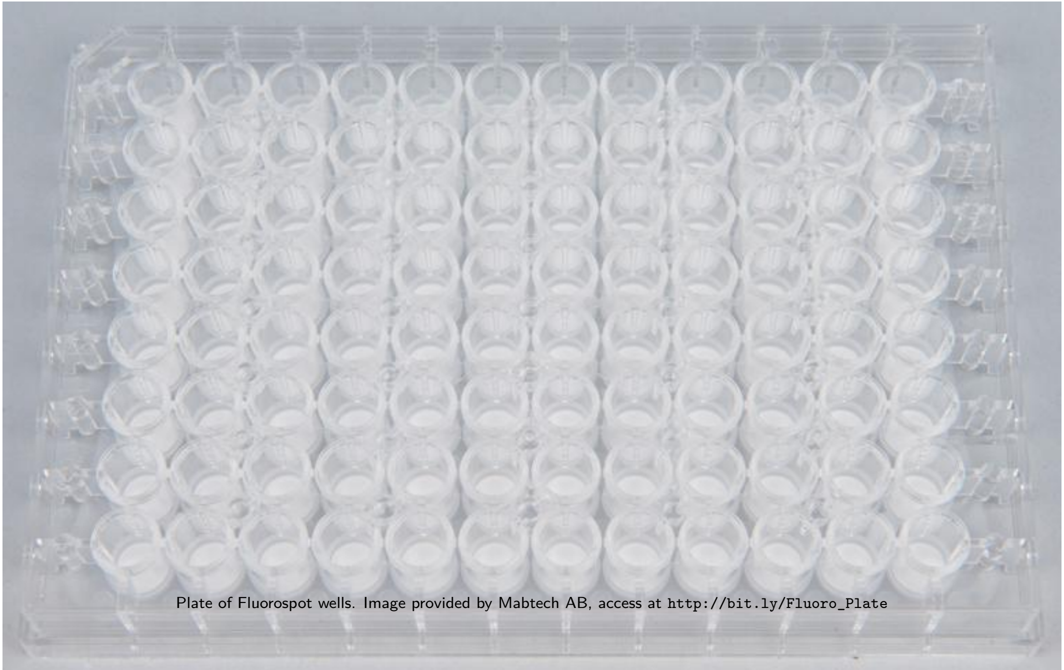
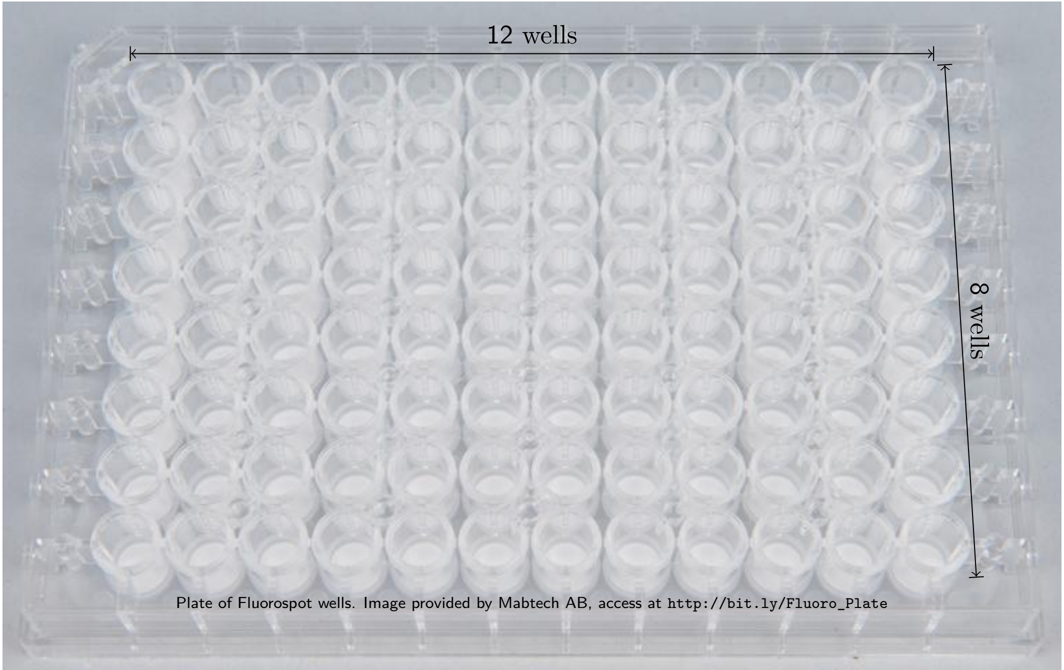


Plate of Fluorospot wells. Image provided by Mabtech AB, access at `http://bit.ly/Fluoro_Plate`



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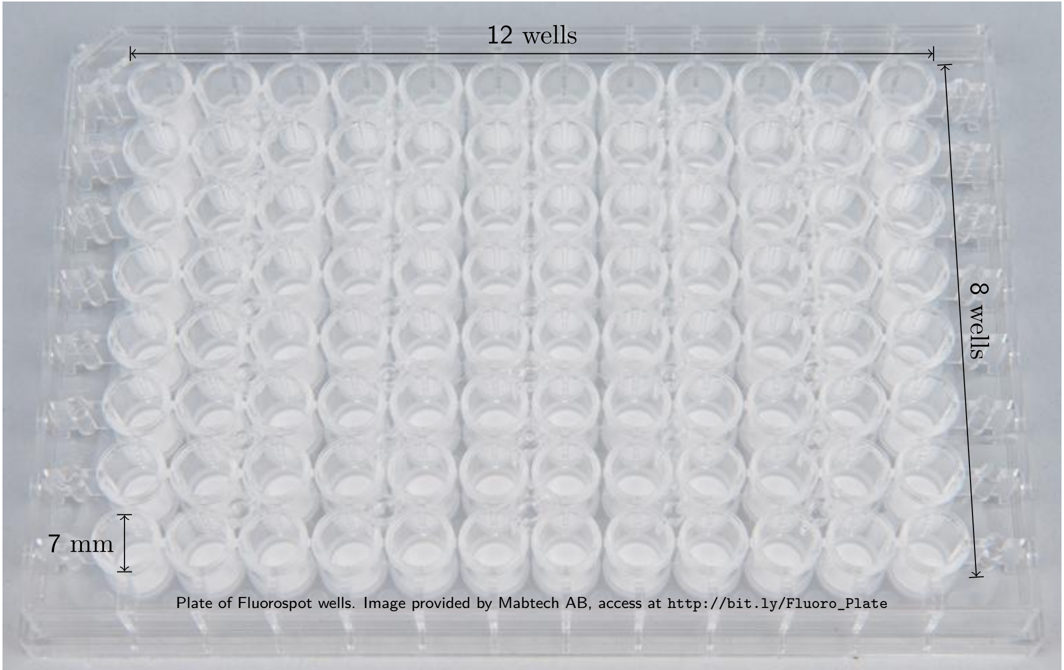

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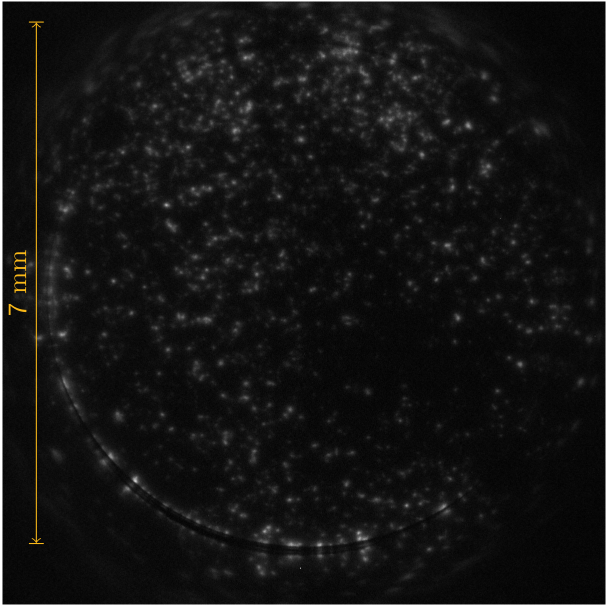
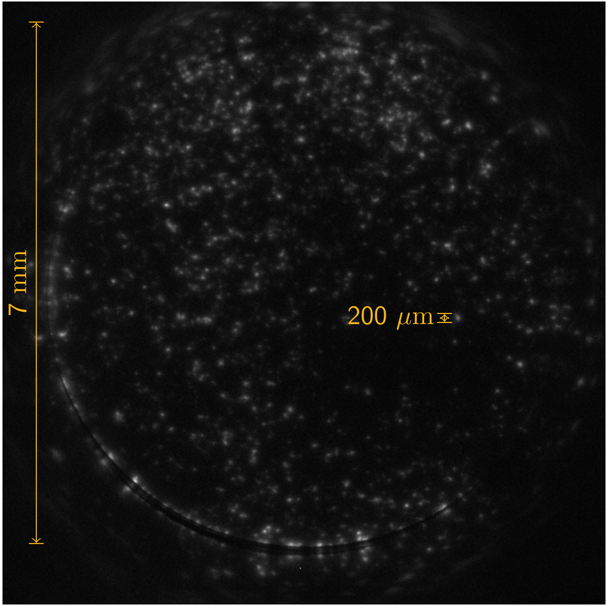


Fluorospot image, provided by Mabtech AB



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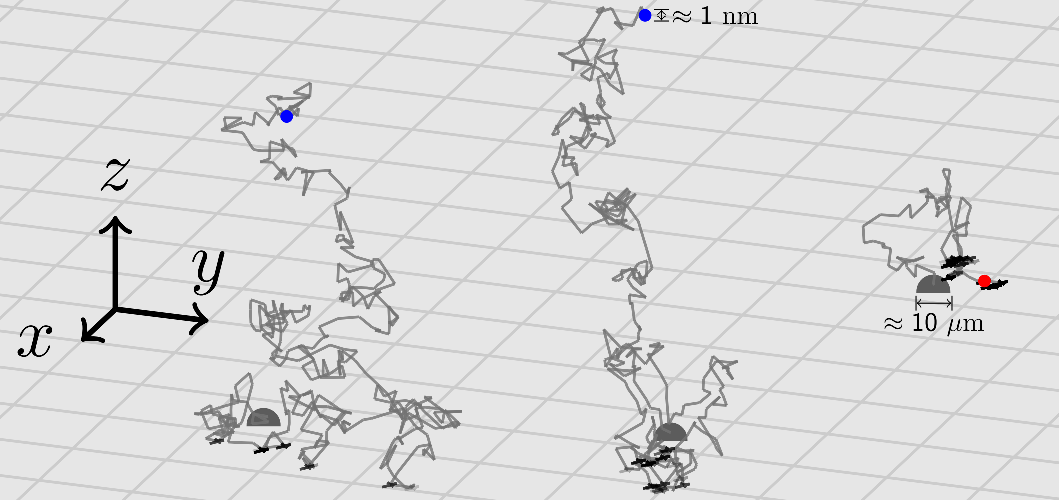
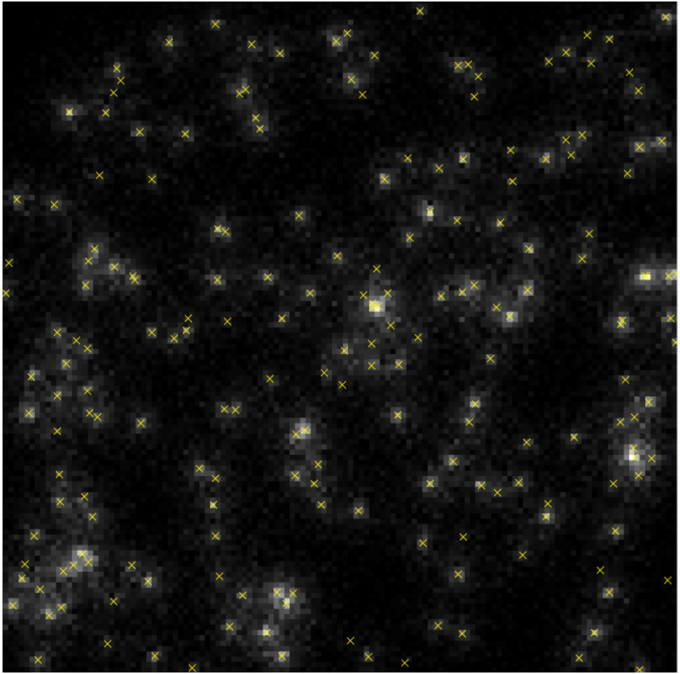

≈ 1 nm
z
y
x
$\approx 10\ \mu$m

Only tested on linux platforms using Okular



A Physical Model for Biomedical Assays (Generative Model I)

The image measures the density of bound particles $d : \mathbb{R}^2 \times \mathbb{R}_+ \to \mathbb{R}_+$ at the final time T, giving an image observation $d_{\mathrm{obs}} : \mathbb{R}^2 \to \mathbb{R}_+$ such that $d_{\mathrm{obs}}(x, y) = d(x, y, T)$.

A Physical Model for Biomedical Assays (Generative Model I)

Density of bound particles $d(x, y, t)$, image observation $d_{\mathrm{obs}}(x, y) = d(x, y, T)$.
$d(x, y, t)$ evolves in time coupled to the 3D density of free particles
$c : \mathbb{R}^2 \times \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$

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Density of bound particles $d(x, y, t)$, image observation $d_{\mathrm{obs}}(x, y) = d(x, y, T)$. Coupled to the 3D density of free particles $c(x, y, z, t)$ and to the source density rate of new particles $s : \mathbb{R}^2 \times \mathbb{R}_+ \to \mathbb{R}_+$

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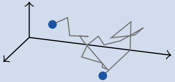
$$\frac{\partial}{\partial t} c = D \Delta c \,,$$

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

$$-D \frac{\partial}{\partial z} c\Big|_{z=0} = s - \frac{\partial d}{\partial t} \,.$$



This physical model was presented before[1], also for ELISPOT[2] and Fluorospot.

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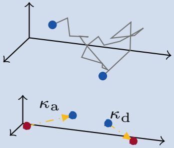

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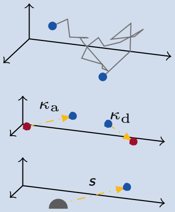

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An Observation Model for Biomedical Assays (I) (Generative Model II)

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

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

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with $a \in \mathcal{A}_+ = \left(\mathrm{L}^2_+\left(\mathbb{R}^2 \times \mathbb{R}_+\right), (\mu\,\cdot, \mu\,\cdot)\right)$ for some mask function $\mu : \mathbb{R}^2 \to \{0, 1\}$, $\sigma_{\mathrm{max}} = \sqrt{2DT}$, $A : \mathcal{A} \to \mathcal{D}$, and

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

- $a(x, y, \sigma)$ is an equivalent of $s(x, y, t)$ where the effect of adsorption and desorption have been summarized.
- Relevantly, $a(x, y, \sigma)$ preserves all the spatial information in $s(x, y, t)$.

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- Relevantly, $a(x,y,\sigma)$ preserves all the spatial information in $s(x,y,t)$.
- The operator A expresses how a becomes d_{obs}, we call it the *diffusion* operator.

An Observation Model for Biomedical Assays (II) (Generative Model II)

$d_{\mathrm{obs}} \in \mathcal{D}_+$, $a \in \mathcal{A}_+$, $A : \mathcal{A} \to \mathcal{D}$ and $d_{\mathrm{obs}} = Aa$, with

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- Independence of Brownian motion in x, y and z.

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- Independence of Brownian motion in x, y and z.
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- $\varphi(\tau, t)$ summarizes effect of adsorption and desorption onto τ for each time of final adsorption t.
- Change variables to those significative to x- and y-movement, $\sigma = \sqrt{2D\tau}$.

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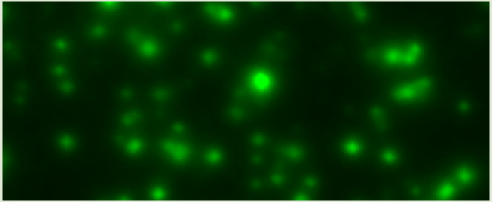
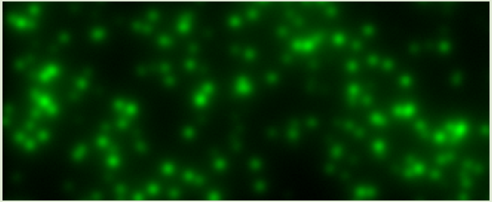
$d_{\mathrm{obs}} \in \mathcal{D}_+$, $a \in \mathcal{A}_+$, $A : \mathcal{A} \to \mathcal{D}$ and

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

Consequences



Real observation (section)



Simulated observation (section)

- Synthetic data
- An inverse problem

Functional Inverse Diffusion (Parameter Learning and Sparsity I)

We have $d_{\mathrm{obs}} \in \mathcal{D}_+$ and want to recover $a \in \mathcal{A}_+$. We propose the (non-smooth, constrained) convex problem

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

with $\xi \in \mathrm{L}^2_+([0, \sigma_{\mathsf{max}}])$, which can be solved by the accelerated proximal gradient algorithm (APG).

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Diffusion Operator, $a \mapsto \int_0^{\sigma_{\max}} G_\sigma a \, \mathrm{d}\sigma$

i) Bound on its operator norm. We use $w \in \mathrm{L}^\infty_+ \left(\mathbb{R}^2\right)$, Jensen's inequality and that $\|G_\sigma\|_{\mathcal{L}(\mathrm{L}^2(\mathbb{R}^2),\mathrm{L}^2(\mathbb{R}^2))} = 1$,

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ii) Adjoint operator. We use that $G_\sigma^* = G_\sigma$,

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

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Non-negatively Constrained Group-Sparsity Regularizer

$$\mathcal{R}(a) = \lambda \left\| \|\xi a_{x,y}\|_{\mathrm{L}^2[0,\sigma_{\max}]} \right\|_{\mathrm{L}^1(\mathbb{R}^2)} + \delta_{\mathcal{A}_+}(a)$$

- Proximal Operator. We use separable sum arguments on the usual prox $\left(\|\cdot\|_{\mathrm{L}^2()}\right)$ derivation, but adding i) the non-negativity constraint and ii) the weighting $\xi(\sigma)$,

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- in detail: Fenchel conjugate, projection on the dual ball (ellipsoid) and Moreau's decomposition.

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- Proximal Operator. Specific case $\xi(\sigma) = i_{\aleph}(\sigma)$ with $\aleph \subset [0, \sigma_{\max}]$ if $p = \mathrm{prox}_{\gamma \mathcal{R}}(a)$, and we decompose $a = a_{\aleph} + a_{\aleph^c}$,

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

Functional Inverse Diffusion (Parameter Learning and Sparsity II)

Require: Initial $a^{(0)} \in \mathcal{A}_+$, image observation $d_{\mathrm{obs}} \in \mathcal{D}_+$

Ensure: A solution $a_{\mathrm{opt}} \in \mathcal{A}_+$

$b^{(0)} \leftarrow a^{(0)}$, $i \leftarrow 0$

repeat

$\quad i \leftarrow i + 1$, $\alpha \leftarrow \frac{t(i-1)-1}{t(i)}$

$\quad a^{(i)} \leftarrow \left[b^{(i-1)} - \eta A^* \left(A b^{(i-1)} - d_{\mathrm{obs}} \right) \right]_+$

$\quad a^{(i)}_{\aleph} \leftarrow a^{(i)}_{\aleph} \left(1 - \dfrac{\eta}{2} \lambda \left\| a^{(i)}_{\aleph,x,y} \right\|^{-1}_{\mathrm{L}^2(\aleph)} \right)_+$

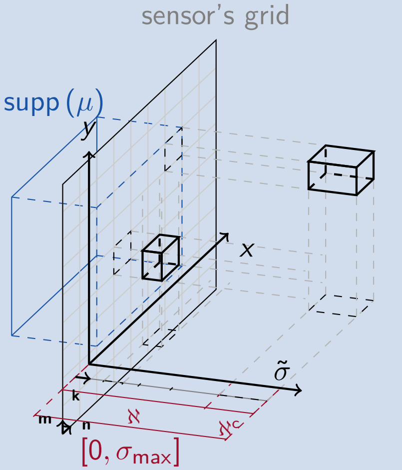
$\quad b^{(i)} \leftarrow a^{(i)} + \alpha \left(a^{(i)} - a^{(i-1)} \right)$

until convergence

$a_{\mathrm{opt}} \leftarrow a^{(i)}$

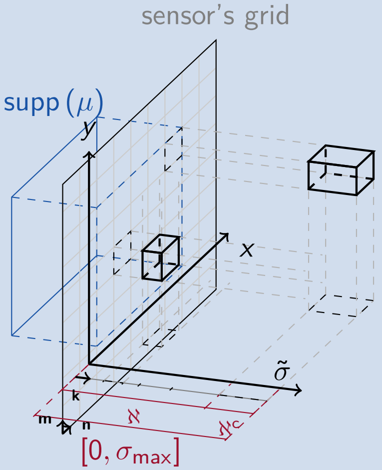
APG algorithm for functional inverse diffusion. Case $\xi(\sigma) = i_{\aleph}(\sigma)$ with $\aleph \subset [0, \sigma_{\mathsf{max}}]$. $\eta = \sigma_{\mathsf{max}}^{-1} \|w\|^{-2}_{\mathrm{L}^\infty(\mathbb{R}^2)}$ for clarity.

Discretization



- Spatial grid given by camera sensor

Discretization



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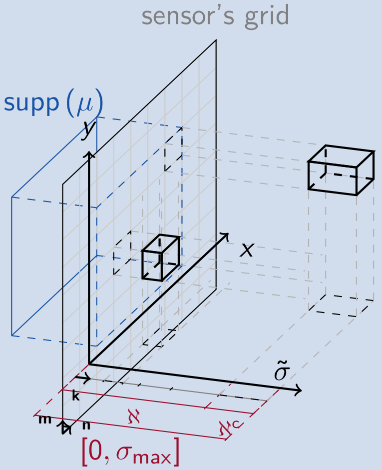

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- Inner approximation paradigm (step-constant functions)

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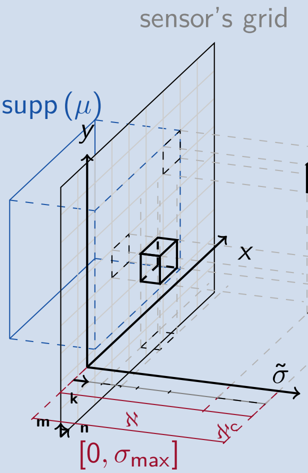

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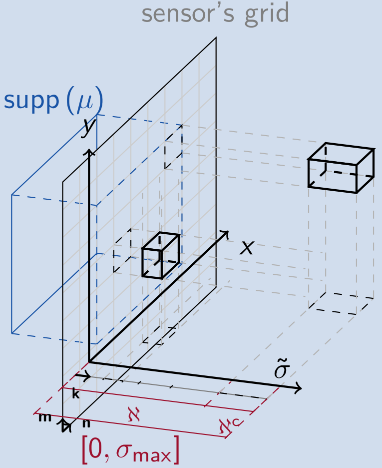

- Spatial grid given by camera sensor
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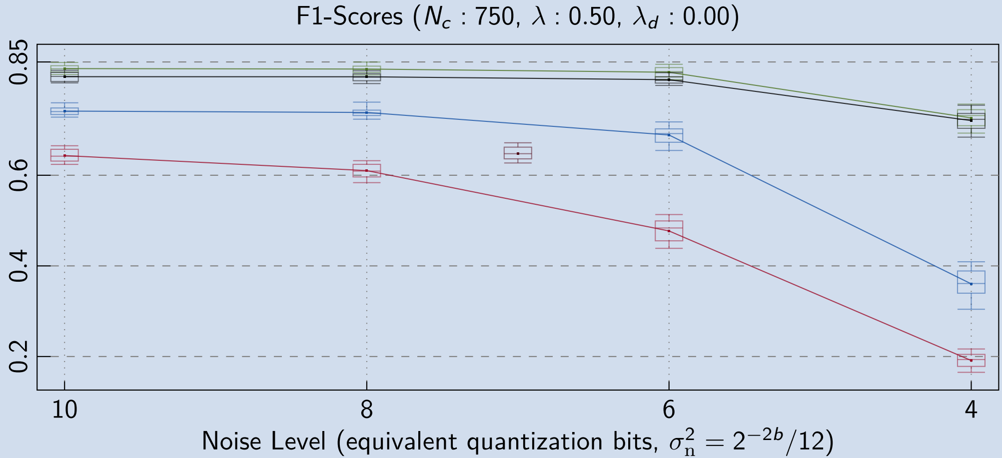
- Inner approximation paradigm (step-constant functions)
- Choice of normalization in restriction and extension operators to ensure norm equivalence
- Resulting algorithm can be reasoned as APG for a discretized model

Results on Synthetic Data



$\mathrm{pre} = \frac{\mathrm{TP}}{\mathrm{TP}+\mathrm{FP}}$, $\mathrm{rec} = \frac{\mathrm{TP}}{\mathrm{TP}+\mathrm{FN}}$, and $\mathrm{F1} = \frac{2\,\mathrm{pre}\cdot\mathrm{rec}}{\mathrm{pre}+\mathrm{rec}}$, computed by detection tolerance of 3 pix, 10000 iterations and the best thresholding, on 512×512 images with 750 active cells. Rank 3 (green) and 1 (black) approximations. Deconvolution (blue).

Thank you

Please, feel free to ask questions.

Thanks to Math @ KTH: Dr. Holger Kohr, Dr. Johan Karlsson, Dr. Ozan Öktem, and Axel Ringh.