Some Statistics for Live Biological Cells

Drift estimation in sparse sequential dynamic imaging and circular scale space theory

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Introduction

- Assessing micro and nano structures in living cells,
- e.g. the cytoskeleton,
- consisting of actin-myosin bundles, intermediate filements and microtubules.
- Statistical tasks
    - feature extraction
    - feature analysis

Introduction

- Assessing micro and nano structures in living cells,
- e.g. the cytoskeleton,
- consisting of actin-myosin bundles, intermediate filements and microtubules.
- Statistical tasks
  - feature extraction
  - feature analysis
- leading to
  1. a stochastic deconvolution model with asymptotics in the sparsity for image enhancement and
  2. the circular or Wrapped SiZer feature analysis with application to stem cell diversifiction.

Image Enhancement for the Microtubles Skeleton

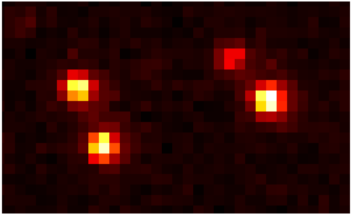
- Objective: fine in vivo structure resolution
  - structural cell network
  - in mitotic spindle
  - cell division
  - cancer treatment
  - here: β-tubulin
- Method: flourescence imaging (visible light)
- Width $\approx$ 25 nm
- Challenge: Abbe (1873) diffraction barrier

$$d \approx \frac{\lambda}{2 \text{ numerical aperture}} \geq 200 \text{ nm}$$

Overcoming Abbe's Limit

- Several methods developed in the last decades, 4PI, STED, SMS, etc., cf. Hell (2007)
- SMS = single marker switching (also known as PALM by Betzig et al. (2006), STORM by Rust et al. (2006), PALMIRA by Egner et al. (2007)):
  1. One laserbeam provides energy for photon emission,
  2. another low energy laserbeam excites (ideally) a single molecule (switch on) which then emits photons for a while (until it switches itself off),
  3. confocally record photon origin,
  4. estimate with high precision center of a Gaussian,
  5. GoTo 2
- precision $\sim$ number of photons
- $\rightarrow$ waiting time
- $\rightarrow$ drift blur.

Single Molecule Localization



Left: ≈ 140 nm resolution. (individual protein ≈ 2 nm)

Right ≈ 20 nm resolution

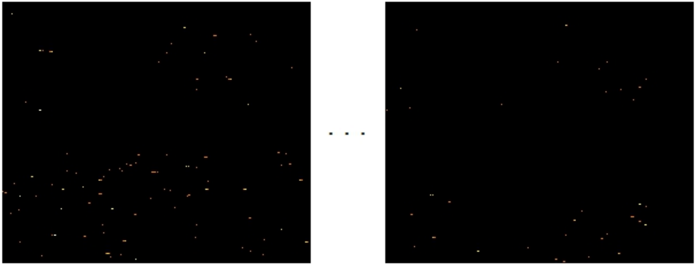
PALMIRA (Egner et al. (2007)): Photoactivated localization microscopy with independently running acquistion:

- Acquistion time ≈ few minutes,
- to account for drift effects an always (over)shining *bead* is introduced.
- Can we do without a bead?

Challenge

- Classical drift (motion) estimation assumes to observe the (noisy) entire image each time point
- Here: only noisy few image pixel observations per time point

First and last single images of PALMIRA data



Challenge and Plan

- Classical drift (motion) estimation assumes to observe the (noisy) entire image each time point
- Here: only noisy few image pixel observations per time point
- Geisler et al. (2012) introduced a general model free practical method
- Here: Gaussian (approximation) model and statistical features via Fourier methods
  - linearly superimpose image in the Fourier domain
  - linear drift becomes shift in the Fourier domain
- Novel asymptotics:
  - $\sharp\{\text{time points}\} \nearrow$
  - image sparsity $\nearrow$

A Few Observation's Drift Model

The few oberservation's regression model

$$y_{j_l^t,t} \;=\; f\big(x_{j_l^t} - \delta_t\big) + \sigma_{j_l^t,t}\epsilon_{j_l^t,t}, \;\; \epsilon_{j_l^t,t} \overset{i.i.d}{\sim} \mathcal{N}(0,1),\; \sigma_{j_l^t,t} > 0$$

with

- f: unknown true image intensity,
- observed image intensities $y_{j_l^t,t}$ at
- time points $t \in \mathbb{T} := \left\{0, \frac{1}{T}, \frac{2}{T}, \dots, \frac{T-1}{T}\right\}$ ($T > 0$),
- for each t, at few $x_{j_l^t}$ ($l = 1, \dots, n_t \approx$ constant, some binning) locations of n uniform pixel locations $\in [0,1]^2$
- δ_t: 2D pixel location valued drift,

has the discrete Fourier transform

$$Y_k^t = f_k^t + \frac{\sigma}{\sqrt{n_t}} W_k^t, \quad k \in \mathbb{Z}^2$$

for each t with

- i.i.d. (standard) complex normals W_k^t.

Novel Asymptotics

The Fourier model:

$$Y_k^t = f_k^t + \frac{\sigma}{\sqrt{n_t}} W_k^t, \quad k \in \mathbb{Z}^2, \quad t = 0, \frac{1}{T}, \ldots, \frac{T-1}{T}$$

where

- n fixed (some binning s.t. n_t fixed, constant and only few single molecules),
- denoting $\sigma/\sqrt{n_t}$ by σ,
- exploiting the shift property:

$$f_k^t = f(\cdot - \delta_t)_k = \underbrace{e^{-2\pi i \langle k, \delta_t \rangle}}_{=:h_k(-\delta_t)} f_k$$

- $T \to \infty$,

motivates the sequence model

$$Y_k^t = h_k(-\delta_t) f_k + \sigma\, W_k^t, \quad k \in \mathbb{Z}^2, \quad t = 0, \frac{1}{T}, \ldots, \frac{T-1}{T}\,.$$

Semiparametric Estimation

Parametric drift model: $\delta_t = \delta_t^\vartheta, \quad \vartheta \in \Theta$ compact $\subset \mathbb{R}^d$
(Sparse) sequence model: $Y_k^t = h_k(-\delta_t^\vartheta) f_k + \sigma W_k^t$
Contrast functionals (empirical, population):

$$\begin{aligned}
M_T(\vartheta) &:= \frac{1}{T} \sum_{|k|<\xi_T} \sum_{t\in\mathbb{T}} \left| h_k(\delta_t^\vartheta)\, Y_k^t - \frac{1}{T} \sum_{t'\in\mathbb{T}} h_k(\delta_t^\vartheta)\, Y_k^{t'} \right|^2 \\
&= \sum_{|k|<\xi_T} \left(\frac{1}{T} \sum_{t\in\mathbb{T}} \left| h_k(\delta_t^\vartheta)\, Y_k^t \right|^2 - \left| \frac{1}{T} \sum_{t'\in\mathbb{T}} h_k(\delta_{t'}^\vartheta)\, Y_k^{t'} \right|^2 \right) \\
&= M_T^0 + \widetilde{M}_T(\vartheta) \\
M(\vartheta) &:= \sum_{k\in\mathbb{Z}^2} \int_0^1 \left| h_k(\delta_t^\vartheta - \delta_t^{\vartheta_0})\, f_k - \int_0^1 h_k(\delta_{t'}^\vartheta - \delta_{t'}^{\vartheta_0})\, f_k dt' \right|^2 dt \\
&= \sum_{k\in\mathbb{Z}^2} |f_k|^2 \left(1 - \left| \int_0^1 h_k(\delta_t^\vartheta - \delta_t^{\vartheta_0})\, dt \right|^2 \right) = M^0 + \widetilde{M}(\vartheta)
\end{aligned}$$

Estimators and Assumptions

For given $T > 0$ and choice of $\xi_T > 0$,

- drift estimator: $\hat{\vartheta}_T \in \arg\min_{\vartheta\in\Theta} M_T(\vartheta)$
- image estimator: $\hat{f}_T(x) := \sum_{|k|<\xi_T} \frac{1}{T} \sum_{t\in\mathbb{T}} h_k(\delta_t^{\hat{\vartheta}_T})\, Y_k^t\, e^{2\pi i\langle k,x\rangle}$.

Assumptions:

- δ_t^{ϑ} = polynomial of fixed degree in t with coefficients determined by $\vartheta \in \Theta$.
- for $\rho = 1$

$$f \in H^{\rho}([0,1]^2) := \left\{ f \in L^1([0,1]^2) : \sum_{k\in\mathbb{Z}^2} (1+|k|^2)^{\frac{\rho}{2}} |f_k|^2 < \infty \right\}$$

- $\exists k_1, k_2, k_1', k_2', k_1'', k_2'', k_1''', k_2''' \in \mathbb{Z}$ such that $k_1 k_2' - k_2 k_1' \neq 0 \neq k_1'' k_2''' - k_2'' k_1'''$, have no common divisors and $|f_k| \neq 0\ \forall k \in \{(k_1,k_2),(k_1',k_2'),(k_1'',k_2''),(k_1''',k_2''')\}$.

Consistency

Theorem 1

Under the assumptions, if $\xi_T \xrightarrow{T\to\infty} \infty$ *and* $\xi_T = o(\sqrt{T})$ *then*

$$\hat\vartheta_T \xrightarrow{a.s.} \vartheta_0 \text{ (population minimizer)}, \ \left\|\hat f_T - f\right\|_2 \xrightarrow{p} 0 \ (T\to\infty)\,.$$

If even $\xi_T = o(T^{1/4})$ *then* $\left\|\hat f_T - f\right\|_2 \xrightarrow{a.s.} 0.$

Proof.

To see $\hat\vartheta_T \stackrel{a.s.}{\to} \vartheta_0$ show

(1) uniqueness of the constrast minimizer ϑ_0

(2) continuity of $\vartheta \mapsto \widetilde{M}(\vartheta)$

(3) $\widetilde{M}_T(\vartheta) \stackrel{a.s.}{\to} \widetilde{M}(\vartheta)$ uniformly in ϑ as $T, \xi_T = o(\sqrt{T}) \to \infty$

Finally show that the order of $\|\hat f_T - f\|^2$ is that of

$$\|\hat\vartheta_T - \vartheta_0\| \frac{1}{\sqrt{T}} \sum_{|k|<\xi_T} |f_k||k||G_k^T|$$

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Asymptotic Normality

$$0 = \mathrm{grad}_\vartheta \widetilde{M}_T(\hat{\vartheta}_T) = \mathrm{grad}_\vartheta \widetilde{M}_T(\vartheta_0) + \mathrm{Hess}_\vartheta \widetilde{M}_T(\vartheta_0)(\hat{\vartheta}_T - \vartheta_0) + \Big(\mathrm{Hess}_\vartheta \widetilde{M}_T(\vartheta^*) - \mathrm{Hess}_\vartheta \widetilde{M}_T(\vartheta_0)\Big)(\hat{\vartheta}_T - \vartheta_0)$$ with

(1) $\sqrt{T}\,\mathrm{grad}_\vartheta \widetilde{M}_T(\vartheta_0) \xrightarrow{D} \mathcal{N}(0, 16\pi^2\sigma^2\Sigma)$

(2) $\mathrm{Hess}_\vartheta \widetilde{M}_T(\vartheta_0) \xrightarrow{a.s.} 8\pi^2\Sigma$

Asymptotic Normality

Theorem 2

Under $T \to \infty, \xi_T = o(T^{1/4}) \to \infty$, if $\hat{\vartheta}_T \to \vartheta_0$ a.s. and

- $f \in H^\rho([0,1]^2)$ *for* $\rho = 2$
- $\vartheta \mapsto \delta_t^\vartheta$ *is* C^2 *with uniformly bounded derivatives*
- $A_{t,t'}^\vartheta := \mathrm{grad}_\vartheta \langle k, \delta_t^\vartheta \rangle (\mathrm{grad}_\vartheta \langle k, \delta_{t'}^\vartheta \rangle)'$
- $\Sigma := \sum_{k \in \mathbb{Z}^2} |f_k|^2 \left(\int_0^1 A_{t,t}^{\vartheta_0}\, dt - \iint_{[0,1]^2} A_{t,t'}^{\vartheta_0}\, dt\, dt' \right)$

we have

$$\sqrt{T}\Sigma(\hat{\vartheta}_T - \vartheta_0) \xrightarrow{D} \mathcal{N}\left(0, \frac{\sigma^2}{4\pi^2}\Sigma\right) .$$

Proof.

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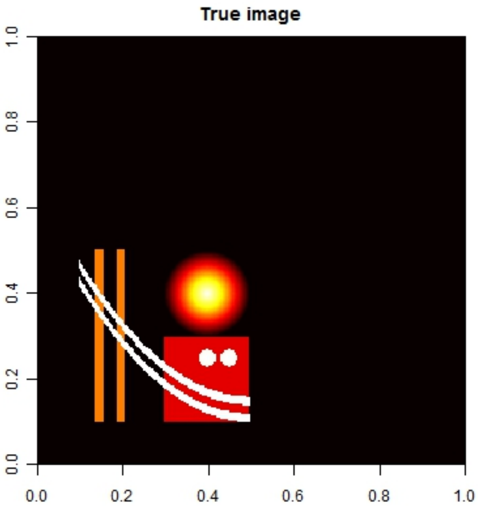
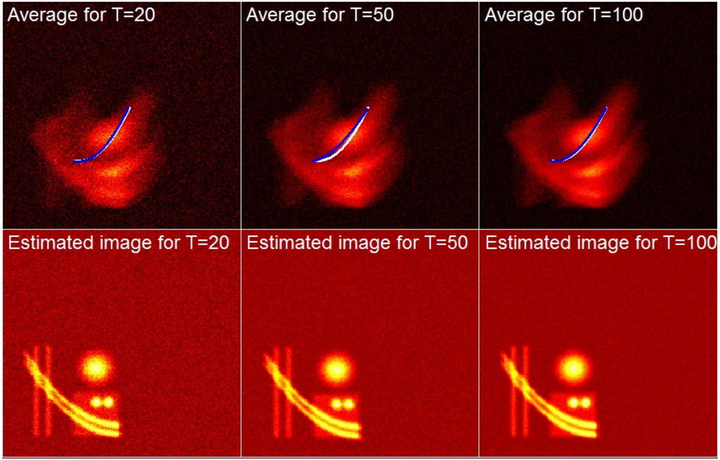
Simulations



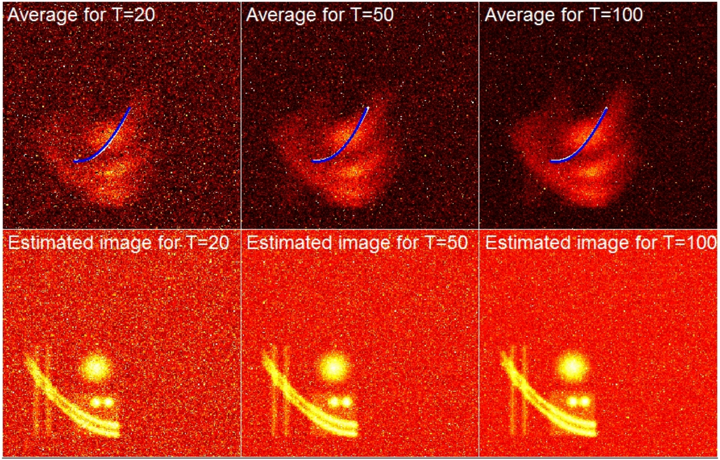
Test image of about $N = 65{,}000$ pixels. For $T \in \{20, 50, 100\}$ select in every single frame randomly $n_t = N/T$ pixels. Original noise level $\sigma = 0.25$.

Simulations



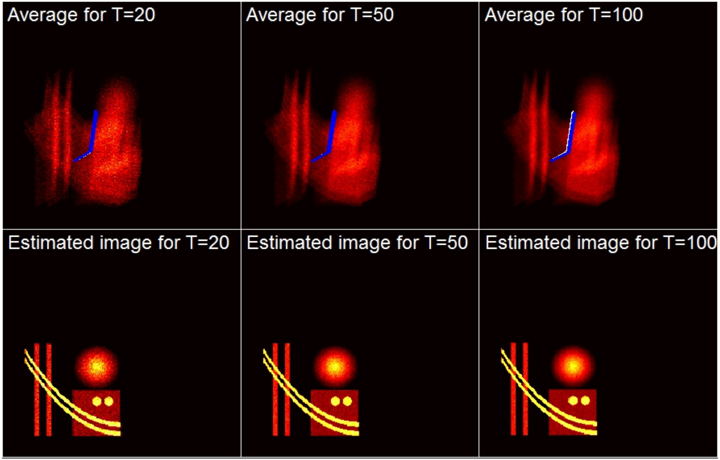
Gauss noise, cubic drift.
White: true drift. Blue: estimated drift.

Simulations



Student t_2 noise, cubic drift.
White: true drift. Blue: estimated drift.

Simulations

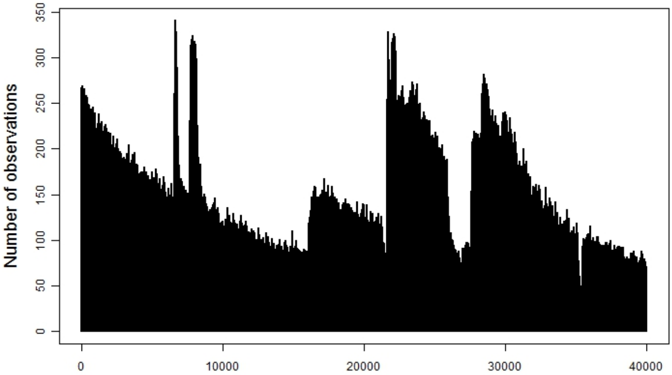


Linear changepoint drift with Poisson noise.
White: true drift. Blue: estimated drift.

Applications to Microtubules-Imaging

RHS-labeled β-tubulin network in a fixed PtK2-cell (male rat kangaroo kidney epithel)

- area: 327×327 nm^2
- frame $\sharp$: $40,000$
- binning: ≈ 100 frames



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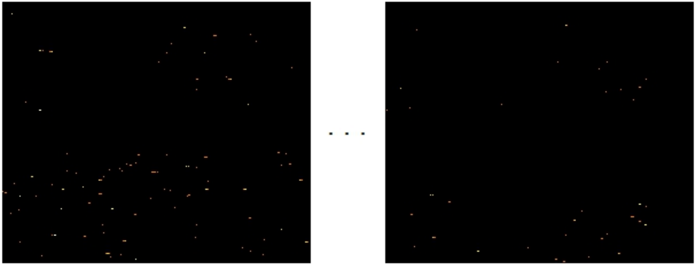
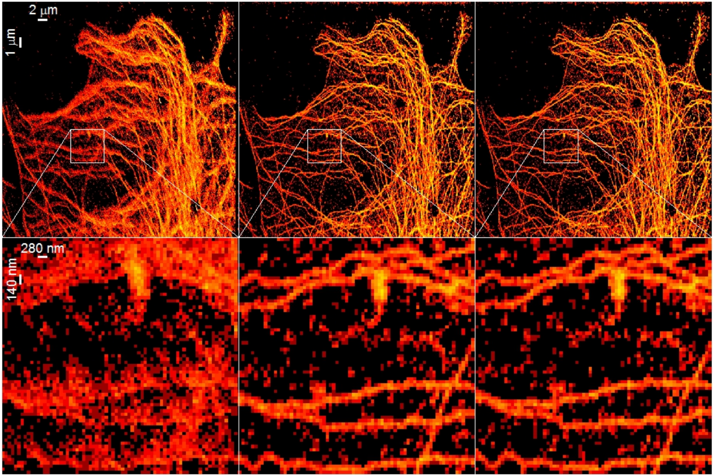
First and last single images of PALMIRA data



Applications in Nanomicroscopy

Raw image | bead tracking | sparse deconvolution



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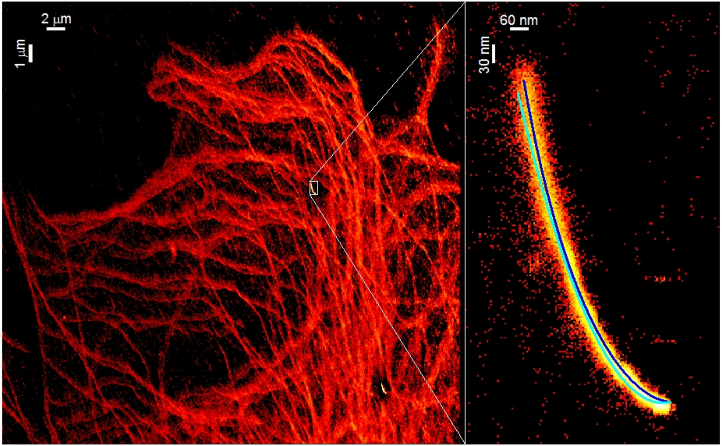
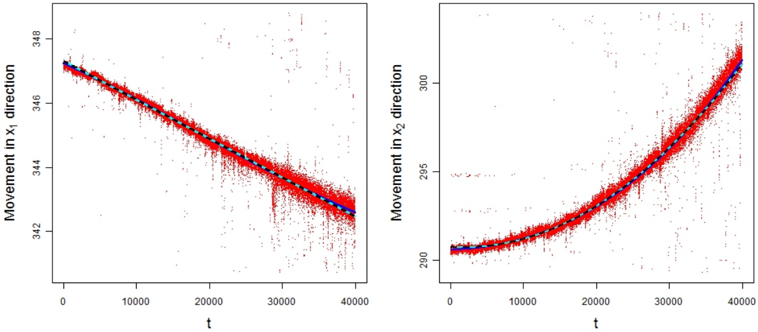


Blue: fit to bead drift. Cyan: overall drift

Bootstrap Confidence Bands

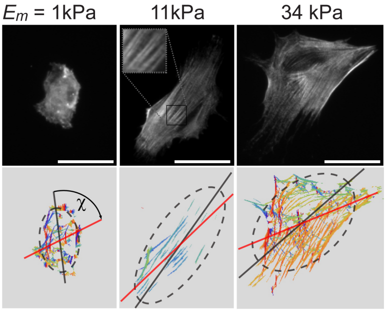


Under the hypothesis of a (low order) polynomial drift, very narrow simultaneous confidence intervals (due to a much larger number of pixel data than of bead data).

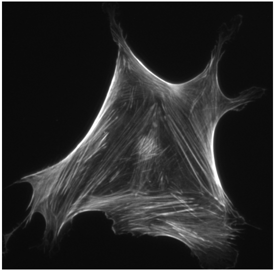
Early Stem Cell Differentiation

- Varying elasticity (kPa),
- soft (neuron, fat, etc.): 1kPa
- medium (muscle) resonance; 11kPa
- hard (bone, scar, etc.): 34 kPa

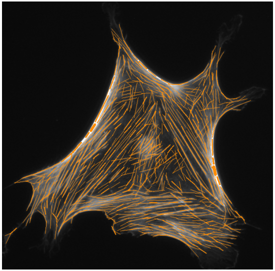
From Zemel et al. (2010)



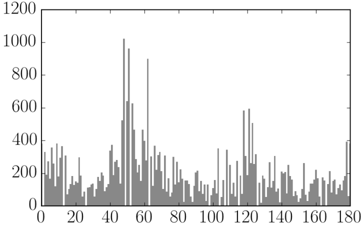
Polarization of Stress Fibres



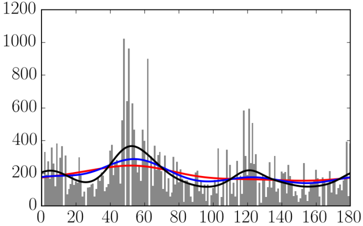
Actin-myosin filament structure



linear filaments extracted



orientation histogram



smoothed histogram

The Linear Scale Space / SiZer of Chaudhuri and Marron (1999, 2000)

- Unknown density $f : \mathbb{R} \to \mathbb{R}^+$,
- f_n its empirical histogram,
- $\hat{f}_n^{(h)} := g^{(h)} * f_n$ its kernel smoothed version,
- $\hat{f}^{(h)} := g^{(h)} * f$ the true kernel smoothed version,
- all with bandwidth $h \in \mathbb{R}^+$.

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- $\hat{f}^{(h)} := g^{(h)} * f$ the true kernel smoothed version,
- all with bandwidth $h \in \mathbb{R}^+$.
- We have confidence that $\hat{f}_n^{(h)}$ has a mode “around” $t \in \mathbb{R}$ if $\exists \epsilon_1, \epsilon_2 > 0$ such that

$$\partial_t \hat{f}_n^{(h)}(t + \epsilon_2) < 0 < \partial_t \hat{f}_n^{(h)}(t - \epsilon_1)$$

with significance.

The Linear Scale Space / SiZer

(a) If $\left(\partial_t \hat{f}_n^{(h)}(t)\right)_{h,t} \to \partial_t f^{(h)}$ weakly

- obtain asymptotic confidence levels for the number modes of $f^{(h)}(t)$.

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(b) If causality holds, i.e.

$$\sharp \text{ modes of } f^{(h)} \leq \sharp \text{ modes of } f^{(h')} \; \forall h \geq h' > 0$$

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Theorem (Chaudhuri and Marron (1999, 2000))

If f is sufficiently regular and $g^{(h)}$ the Gaussian heat kernel then causality holds and

$$\sqrt{n}\left(\partial_t \hat{f}_n^{(h)}(t) - \partial_t \hat{f}^{(h)}(t)\right) \to (G_h)_t \text{ weakly}$$

with a Gaussian process $(G_h)_t$.

The Circular SiZer

Which smoothing kernel on the circle $[-\pi, \pi)$ gives

1. empirical scale space tube $\to$ Gaussian process?
2. causality of the scale space tube?

$\Rightarrow$ confidence bounds from below for number of true modes.

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1. Kernels with second moments, e.g. the von Mises density, making the CircSiZer by Oliveira et al. (2013):

$$m_\kappa(x) := \frac{1}{2\pi\, I_0(\kappa)}\, e^{\kappa \cos(x)}\,.$$

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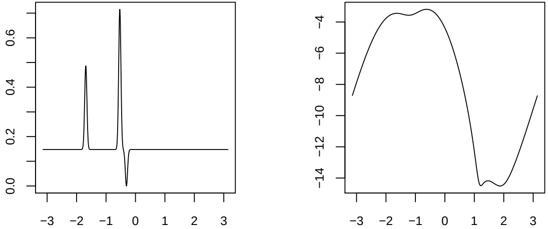
2. The CircSiZer is not causal (cf. also Munk (1999)):



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2. **Theorem 3 (The WiZer)**

The solution of the circular heat equation: the wrapped Gaussian

$$g_h^{(w)}(x) := \sum_{m=-\infty}^{\infty} \frac{1}{\sqrt{2\pi}\, h}\, e^{-\frac{(x+2\pi m)^2}{2h^2}}\,.$$

guarantees causality of the scale space tube.

Circular Scale Space Axiomatics

A family $\{L_h : h > 0\}$ of convolution kernels ($\int L_h = 1$) is

- a semi-group if $L_{h+h'} = L_h * L_{h'}$ for all $h, h' > 0$
- causal if $S(L_h * f) \leq S(f)$ for all f
- strongly Lipschitz if $\exists r > 0$

$$\forall \epsilon > 0 \; \exists h_0 = h_0(\epsilon) > 0 \text{ such that } |(\mathcal{F}L_h)_k - 1| < \epsilon h |k|^r$$

for all $k \in \mathbb{Z}$ and all $0 < h \leq h_0$.

Circular Scale Space Axiomatics

A family $\{L_h : h > 0\}$ of convolution kernels ($\int L_h = 1$) is

- a semi-group if $L_{h+h'} = L_h * L_{h'}$ for all $h, h' > 0$
- causal if $S(L_h * f) \leq S(f)$ for all f
- strongly Lipschitz if $\exists r > 0$

$$\forall \epsilon > 0 \; \exists h_0 = h_0(\epsilon) > 0 \text{ such that } |(\mathcal{F}L_h)_k - 1| < \epsilon h |k|^r$$

for all $k \in \mathbb{Z}$ and all $0 < h \leq h_0$.

Theorem 4

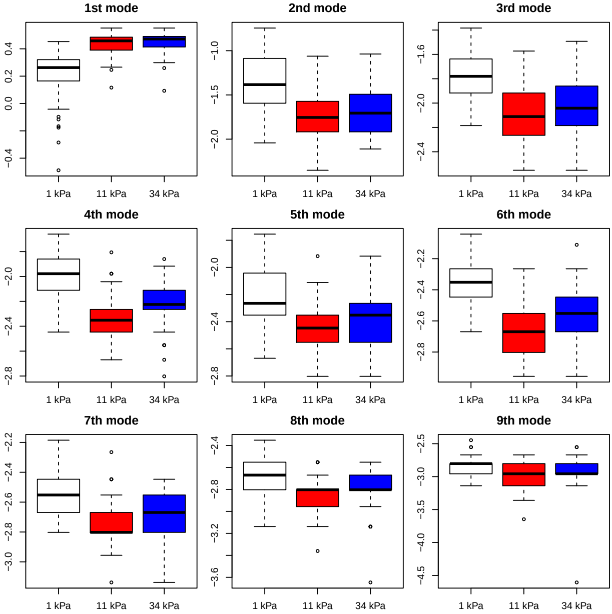
The only casual and strongly Lipschitz semi-group on the circle is given by the wrapped Gaussians.

For Euclidean analogs, e.g. Weickert et al. (1999); Lindeberg (2011).

Persistence of Modes

- Scale spaces allow for definition of persistences:
- WiZer (SiZer) requires a smallest bandwidth (Schmidt-Hieber et al. (2013) does not),
- coming from the other side (large to small bandwidth),
- at some bandwidth the first mode pops up
- persists until the second pops up
- persists until the third ...
- ...

Log Persistences: Boxplots



Discussion

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References

Abbe, E. (1873). Beiträge zur Theorie des Mikroskops und der mikroskopischen Wahrnehmung. *Archiv für mikroskopische Anatomie 9*(1), 413–418.

Betzig, E., G. H. Patterson, R. Sougrat, O. W. Lindwasser, S. Olenych, J. S. Bonifacino, M. W. Davidson, J. Lippincott-Schwartz, and H. F. Hess (2006). Imaging intracellular fluorescent proteins at nanometer resolution. *Science 313*(5793), 1642–1645.

Brown, L. D., I. M. Johnstone, and K. B. MacGibbon (1981). Variation diminishing transformations: A direct approach to total positivity and its statistical applications. *Journal of the American Statistical Association 76*(376), 824–832.

Chaudhuri, P. and J. Marron (1999). Sizer for exploration of structures in curves. *Journal of the American Statistical Association 94*(447), 807–823.

Chaudhuri, P. and J. Marron (2000). Scale space view of curve estimation. *The Annals of Statistics 28*(2), 408–428.

Egner, A., C. Geisler, C. von Middendorff, H. Bock, D. Wenzel, R. Medda, M. Andresen, A. Stiel, S. Jakobs, C. Eggeling, A. Schoenle, and S. W. Hell (2007). Fluorescence nanoscopy in whole cells by asnychronous localization of photoswitching emitters. *Biophysical Journal 93*, 3285–3290.

Geisler, C., H. T., A. Schoenle, S. W. Hell, A. Munk, , and A. Egner (2012). Drift estimation for single marker switching based imaging schemes. *Optics Express 20*(7), 7274–7289.

Hartmann, A., S. Huckemann, J. Dannemann, O. Laitenberger, C. Geisler, A. Egner, and A. Munk (2015). Drift estimation in sparse sequential dynamic imaging: with application to nanoscale fluorescence microscopy. *Journal of the Royal Statistical Society, Series B*. early online access.

Hell, S. W. (2007). Far-field optical nanoscopy. *Science 316*, 1153–1158.

Huckemann, S. F., K.-R. Kim, A. Munk, F. Rehfeld, M. Sommerfeld, J. Weickert, and C. Wollnik (2015). The circular sizer, inferred persistence of shape parameters and application to stem cell stress fibre structures. *Bernoulli*. early online access.

Lindeberg, T. (2011). Generalized gaussian scale-space axiomatics comprising linear scale-space, affine scale-space and spatio-temporal scale-space. *Journal of Mathematical Imaging and Vision 40*(1), 36–81.

Mairhuber, J., I. Schoenberg, and R. Williamson (1959). On variation diminishing transformations on the circle. *Rendiconti del Circolo matematico di Palermo 8*(3), 241–270.

Munk, A. (1999). Optimal inference for circular variation diminishing experiments with applications to the von-mises distribution and the fisher-efron parabola model. *Metrika 50*(1), 1–17.

Oliveira, M., R. M. Crujeiras, and A. Rodríguez-Casal (2013). Circsizer: an exploratory tool for circular data. *Environmental and Ecological Statistics*, 1–17.

Rust, M. J., M. Bates, and X. W. Zhuang (2006). Sub-diffraction-limit imaging by stochastic optical reconstruction microscopy (storm). *Nature Methods 3*, 793–795.

References

Schmidt-Hieber, J., A. Munk, and L. Dümbgen (2013). Multiscale methods for shape constraints in deconvolution: Confidence statements for qualitative features. *Ann. Statist. 41*(3), 1299–1328.

Weickert, J., S. Ishikawa, and A. Imiya (1999). Linear scale-space has first been proposed in Japan. *Journal of Mathematical Imaging and Vision 10*(3), 237–252.

Zemel, A., F. Rehfeldt, A. E. X. Brown, D. E. Discher, and S. A. Safran (2010). Optimal matrix rigidity for stress-fibre polarization in stem cells. *Nat Phys 6*(6), 468–473.