Julia Brettschneider

Statistical methodology and data science in science and engineering:

Point processes

1 Hawkes process modelling of the pandemic

2 Dead pixel formations on digital X-ray detectors

3 Microscopic image based modelling of biological processes

https://warwick.ac.uk/fac/sci/statistics/staff/academic-research/brettschneider/

Applied statistician/data scientists

Collaborators: engineers, life scientists, clinicians…

Domains: genomics, microscopy, detectors, cancer, screening, finance, OR…

Methodological topics: data quality, spatial statistics, decision theory, concepts of probability and risk

Short biography

- Reader (since 2021), Associate Professor (2010-2021), Assistant Professor (2007-2010), Dept of Statistics, University of **Warwick, UK**
- **Turing fellow** since 2017
- Assistant Professor, Dept of Math/Stats & Dept of Community Health/Epidemiology & Cancer Research Institute, **Queen's University, CN**
- Visiting Assistant Professor and Research Statistician, Dept of Statistics at **University of California at Berkeley, USA**
- Postdoctoral fellow in Computational Biology at **Eurandom, NL**
- PhD (2001) in Mathematics, thesis supervisor Prof. H. Föllmer, **Humboldt Uni Berlin, D**
- Masters in Mathematics (with Computer Sciences and Psychology), thesis supervisor Prof. H. Föllmer, **University Bonn, D**

Preamble: mathematical sciences as bridge

> *"The **instrument that mediates between theory and practice**, between thought and observation, is mathematics; it builds the **connecting bridge** and makes it stronger and stronger. Thus it happens that our entire present-day culture, insofar as it rests on intellectual insight into and harnessing of nature, is founded on mathematics."*
>
> David Hilbert

In Königsberg on 8 September 1930, David Hilbert addressed the yearly meeting of the Society of German Natural Scientists and Physicians (Gesellschaft der Deutschen Naturforscher und Ärzte).
Full text of the speech in English and German at url below, including audio file:

http://math.sfsu.edu/smith/Documents/HilbertRadio/HilbertRadio.pdf

Point processes

Definition: Point Process

Point processes are a class of random process whose realisations are a set of points on some given space.

i.e. A sequence of random variables $t = \{t_1, t_2, \ldots, t_d\}$ taking values in a subset of $\mathbb{R}^d$.

Definition: Temporal Point Process

Temporal Point process is a point process over time: It describes the occurrence of random events over time.

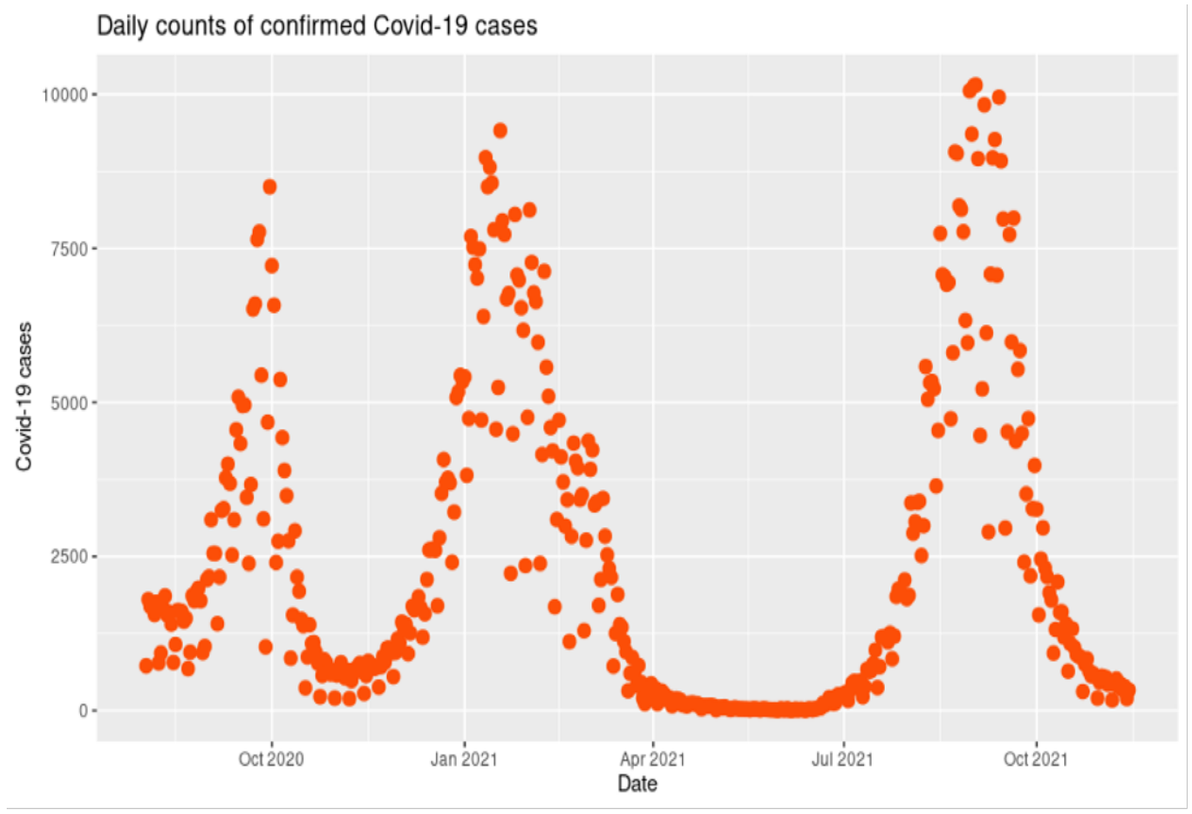
i.e. a sequence of events $t = \{t_1, t_2, \ldots, t_d\}$ s.t. $0 \leq t_1 < t_2 < \ldots < t_d$

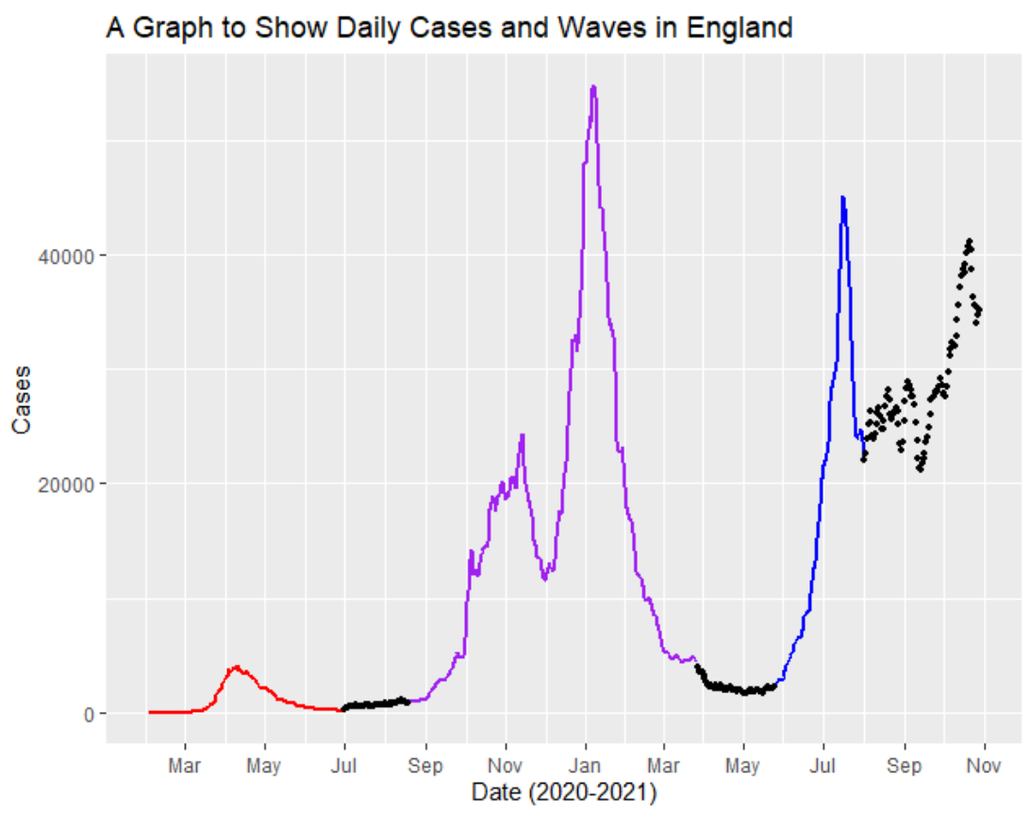
Hawkes process modelling of the pandemic

Joint projects with integrated Master's students on COVID-19 data

1. Data from Israel
Vaccine for data deal with Pfizer/BioNTech
(Marianna Mavroleftherou's project)

2. Data from England
ONS/Oxford survey
(Adam Davison's project)





Hawkes process modelling of the pandemic

Hawkes Process

A Hawkes Process *N* is defined to be a self-exciting temporal point process, where *N(t)* represents the number of events **up to time *t*.**

And is fully described by the conditional intensity function λ:

$$\lambda(t) = \mu + \alpha \sum_{i:t_i<t} y_{t_i}\, g(t - t_i)$$

Background intensity
Or
Baseline mean

Excitation intensity

Triggering kernel
Or
decay function

Hawkes process modelling of the pandemic

Model Setup I

- We want to model the number of cases per day,
  i.e. *Y(t)* where each time period *t* is a day.

- Self – excitation property: Hawkes Process suitable for modelling Covid-19 cases.

Model Setup II

- It is a natural response to assume that ***Y(t)* follows *Poisson(λ(t))***

Since Poisson distribution is governed by one parameter λ, which is the expected number of times an event occurs in an interval of time or space.

Hence, we set:

$$P(Y(t) = y \mid \lambda(t)) = \frac{\lambda(t)^y e^{\lambda(t)}}{y!}$$

- Further to this:

we choose the triggering kernel **g()** to be the **geometric** excitation kernel:

$$g(t - t_i|\beta) = \beta(1 - \beta)^{t - t_i - 1}$$

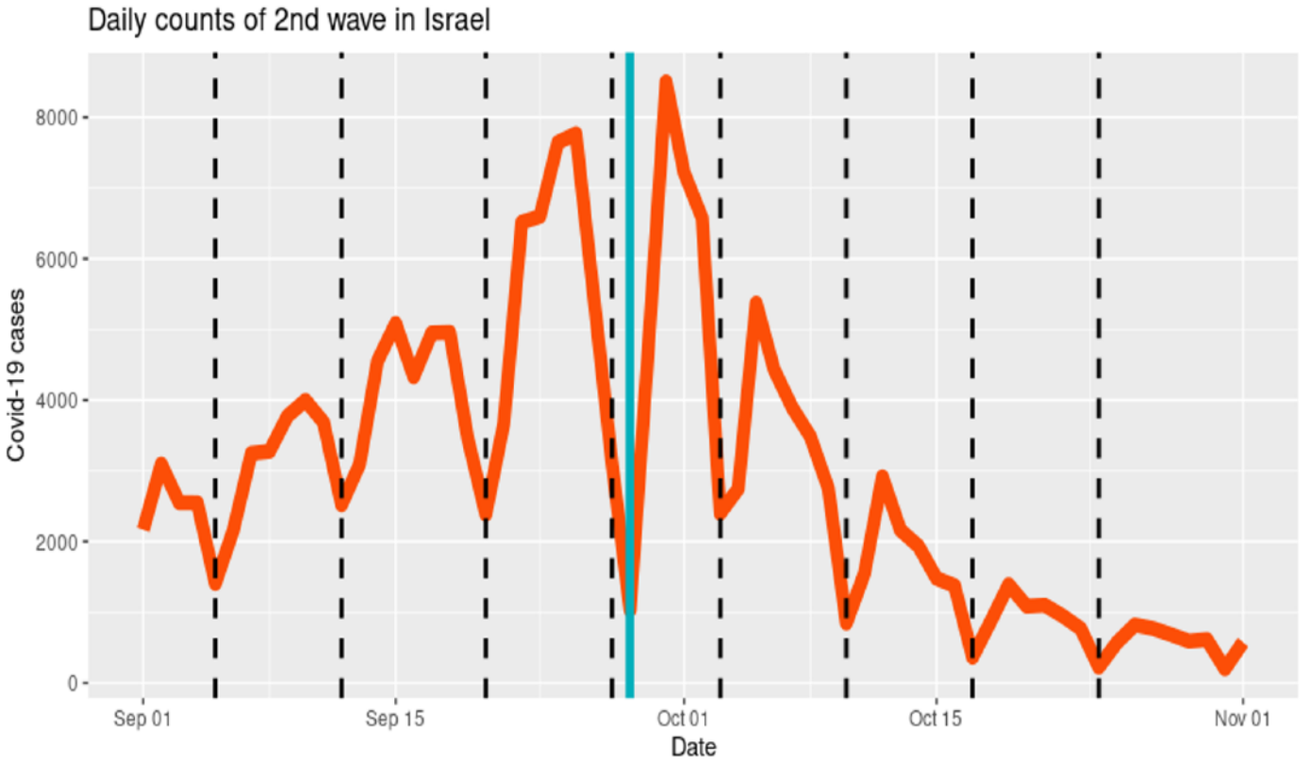
Since it can be shown to be the generalization of the exponential distribution in discrete time.

Hawkes process modelling of the pandemic

Model fitting in practice:

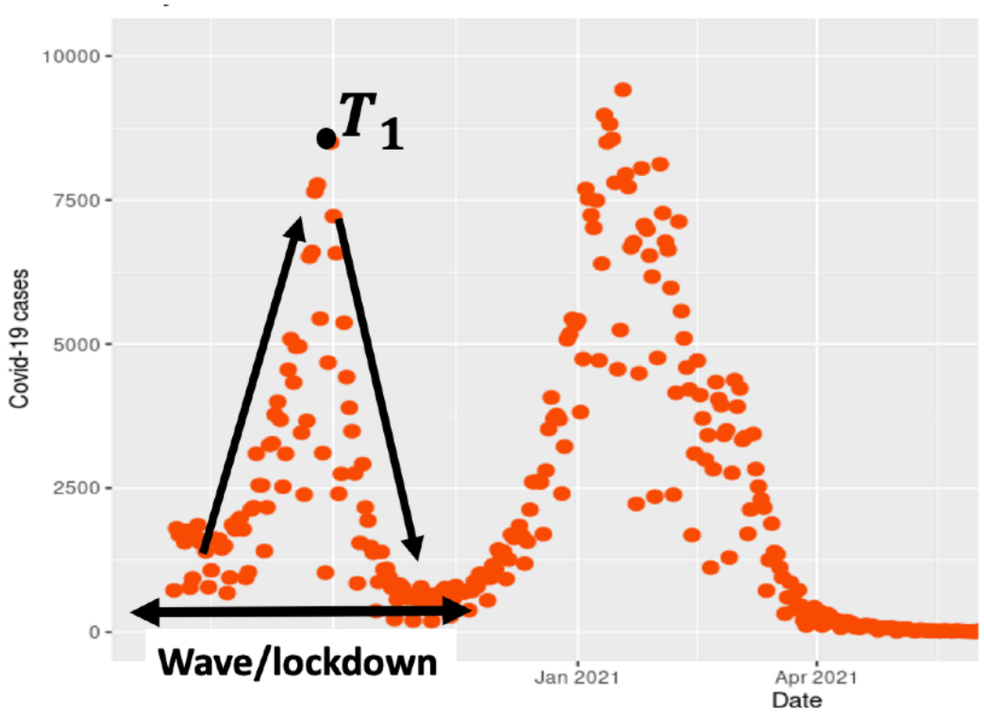
1. Data preprocessing

Small counts, smoothing



2. Waves

Piecewise fitting, piques



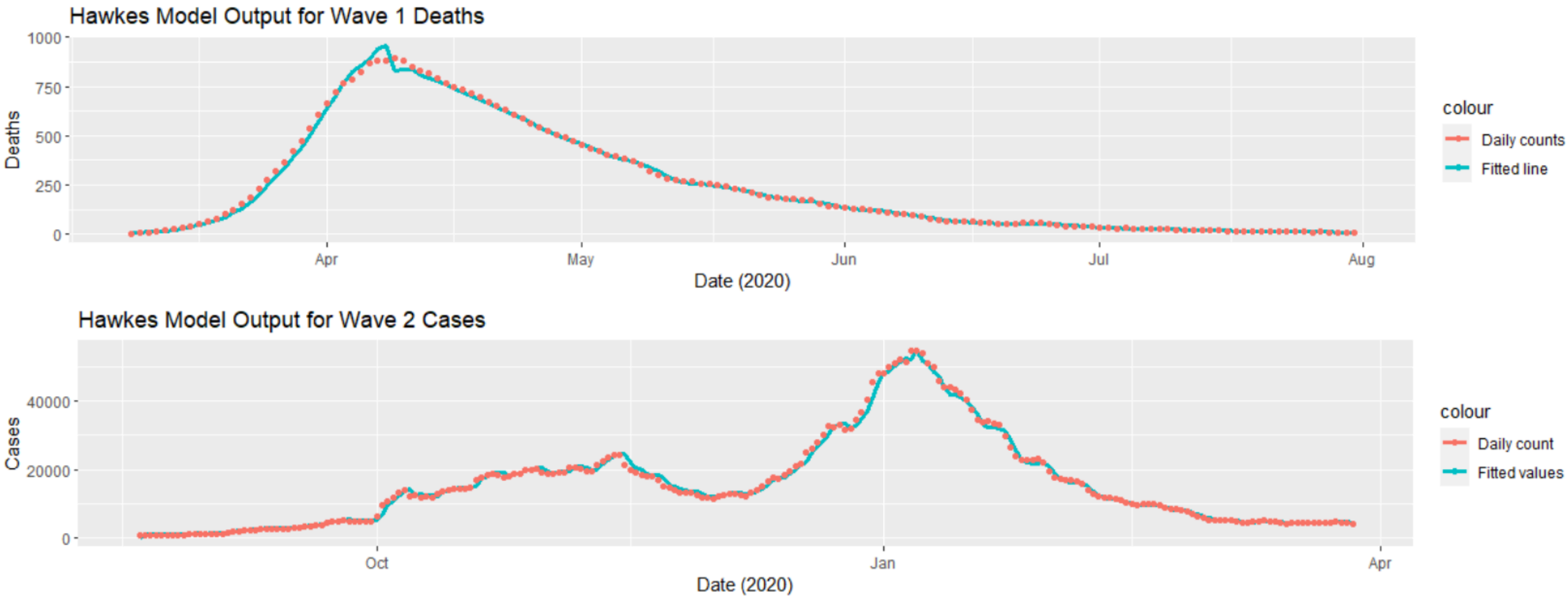
3. Likelihood function

4. Inference

- ML with Nelder-Mead
- Bayesian posterior MCMC

Hawkes process modelling of the pandemic

English data:



Hawkes process modelling of the pandemic

Further and future work:

- Models including age
- Including vaccination rates
- Testing coverage/reliability
- Behavioural indicators (e.g. google searches or mobility)
- Lockdown effects
- Events (e.g. football, holidays) and interaction with other factors
- Mixture population
- Regional models

Dead pixel formations on digital X-ray detectors

Inside-out

Statistical Methods for Computed Tomography Validation of Complex Structures in Additive Layer Manufacturing

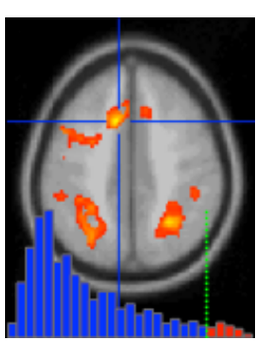
EPSRC grant
3 years

10/2013 -
9/2016

EP/K031066/1

PI: Prof W Kendall
Other investigators: Prof M A Williams, Dr G J Gibbons, Dr J Brettschneider, Prof T Nichols

Further team members: Clair Barnes, Jay Warnett, Audrey Kueh
Industrial partners: Nikon Metrology, Remishaw, EOS systems




Spatial analysis of dead pixels

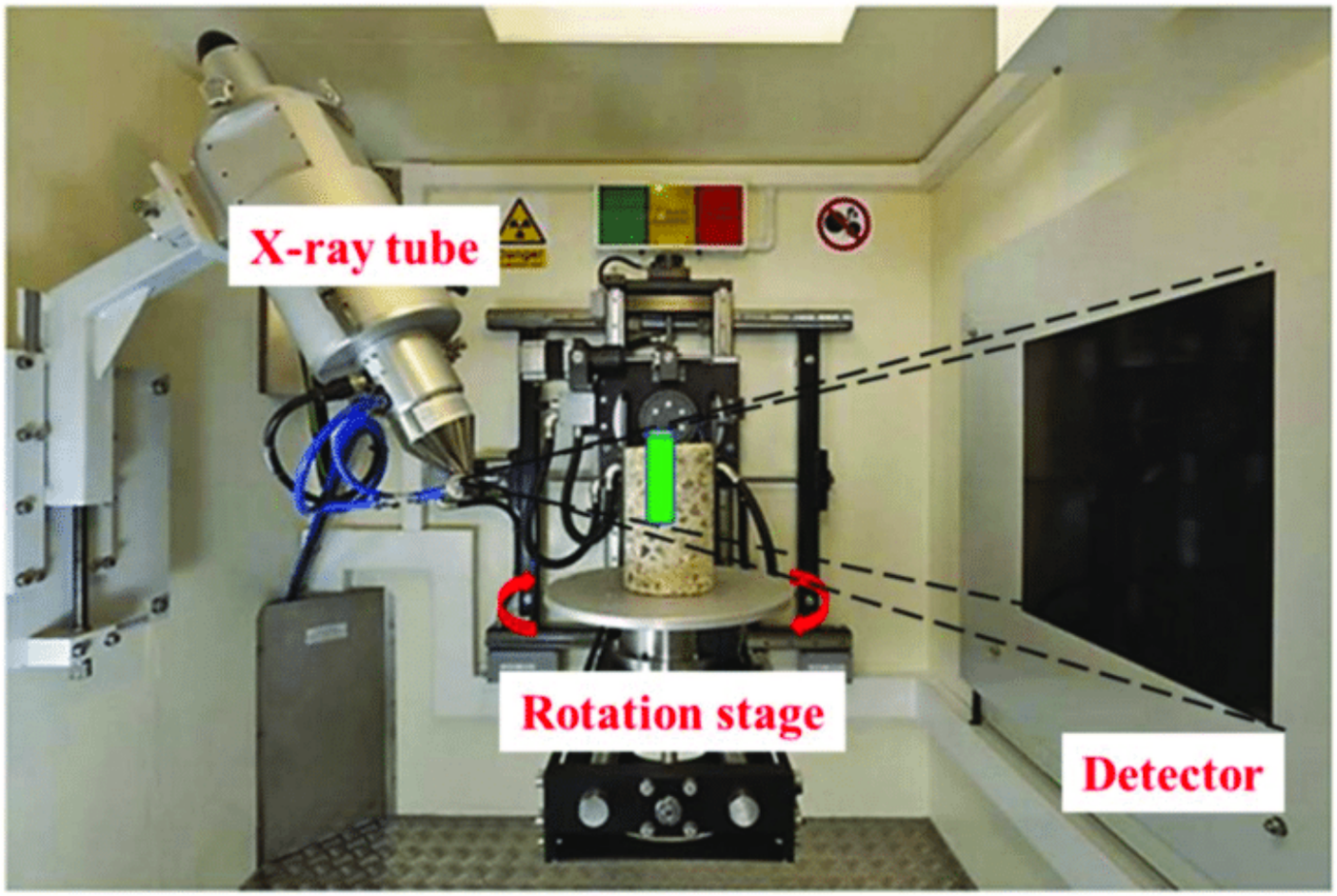
Objectives:

- Feedback about state of detector through spatial pixel damage analysis
- Detector data repository

Applications:

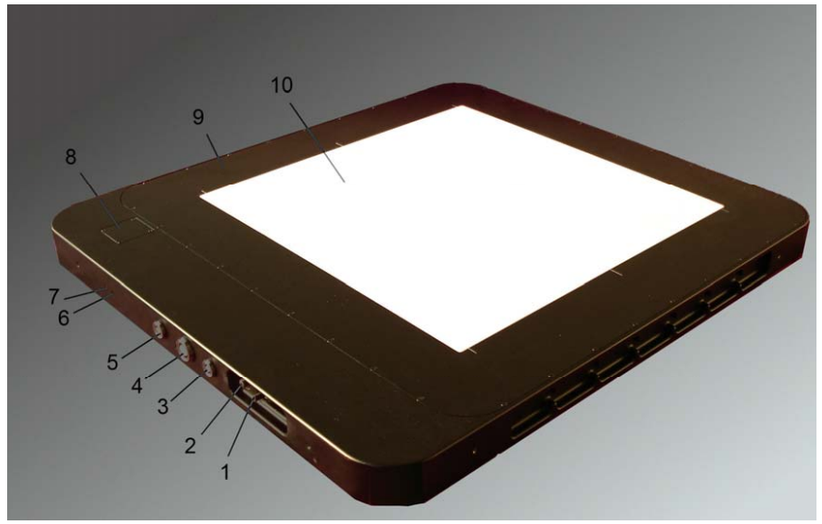
- Identify poor quality regions (patches with high dead pixels density) through density thresholding
- Remaining area CSR means no special causes of poor quality
- Identify causes of poor quality
- Monitor over time
- Conclusions for usage modes
- Conclusions about weakness of detector construction

X-ray chamber

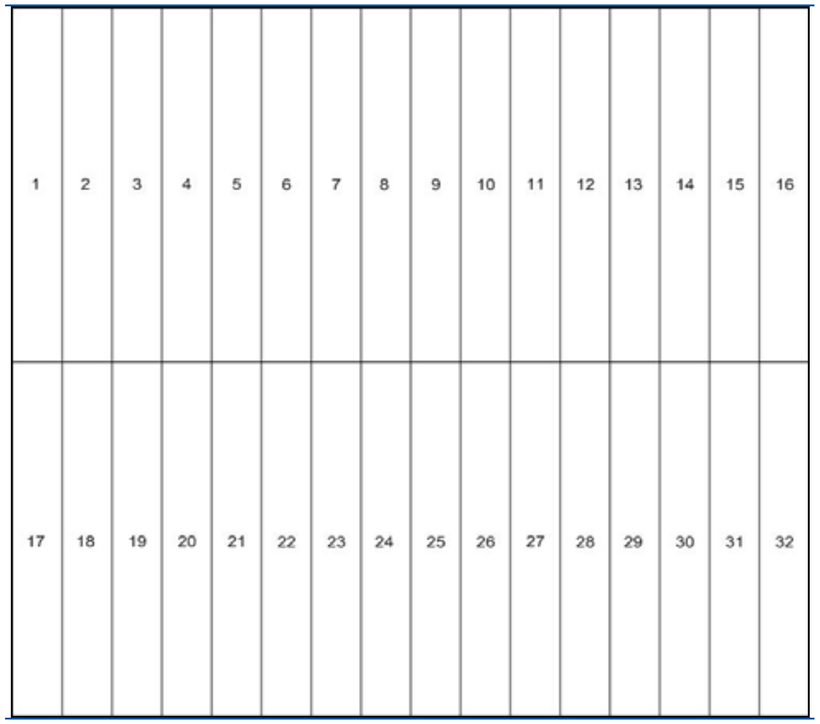


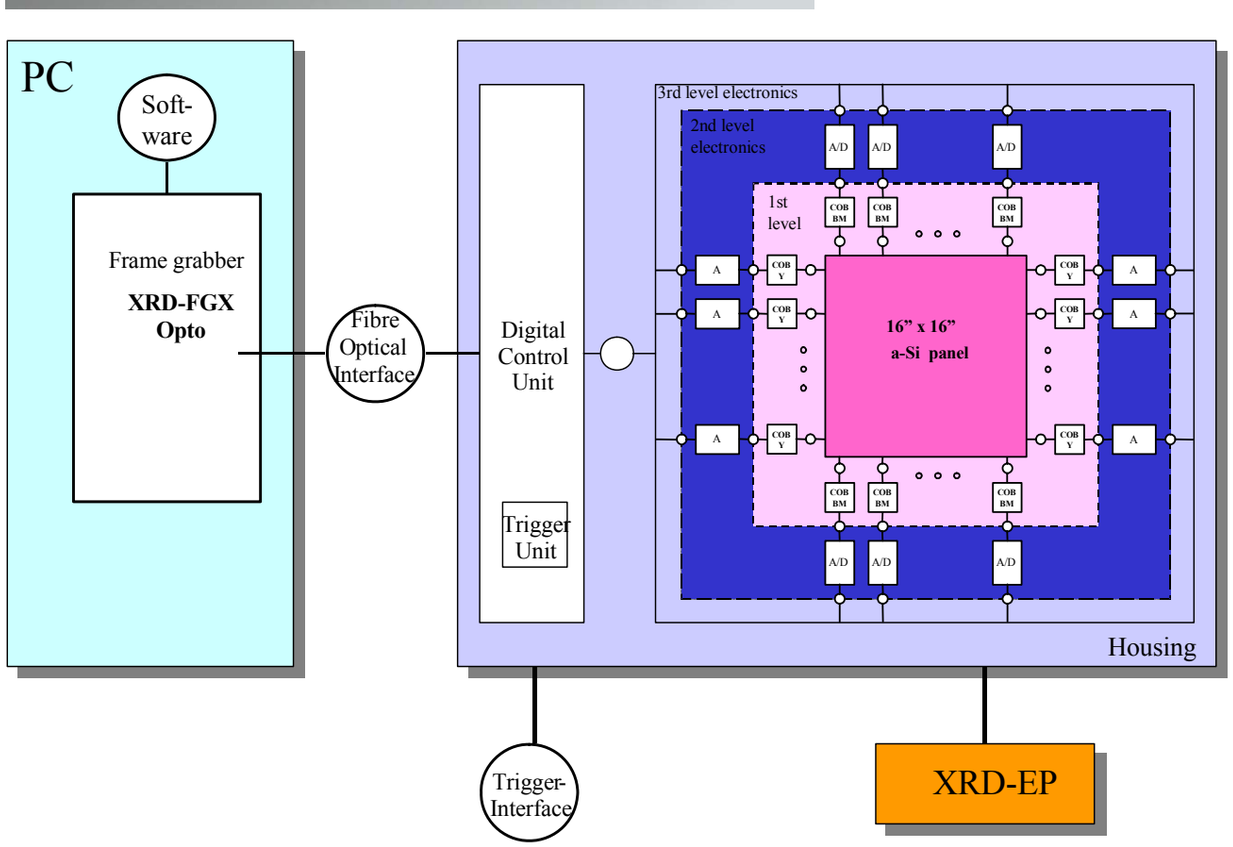
https://www.researchgate.net/figure/Example-of-an-industrial-computed-tomography-CT-system_fig1_324511614

X-ray detector



Perkin Elmer
XRD 1621

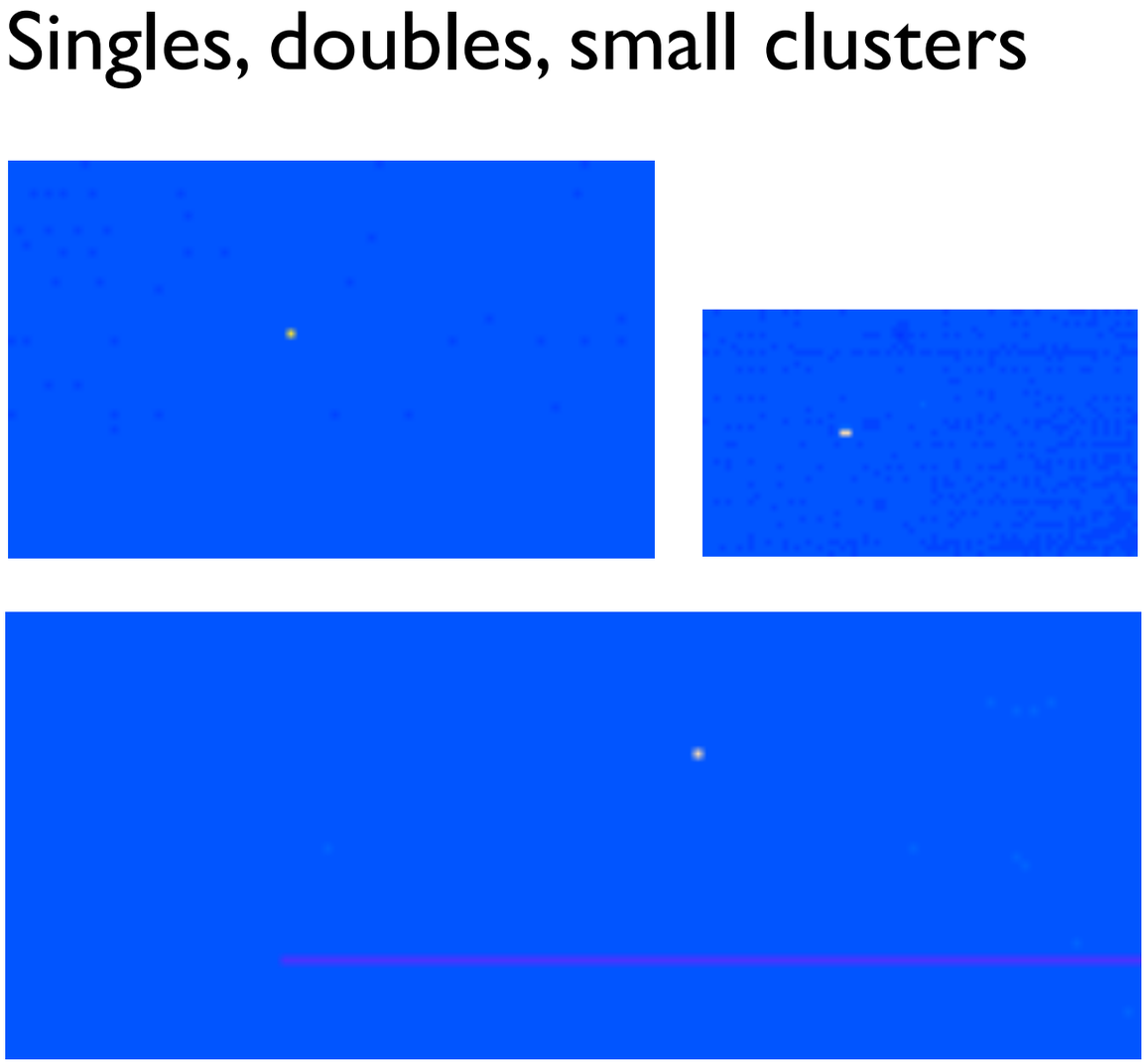




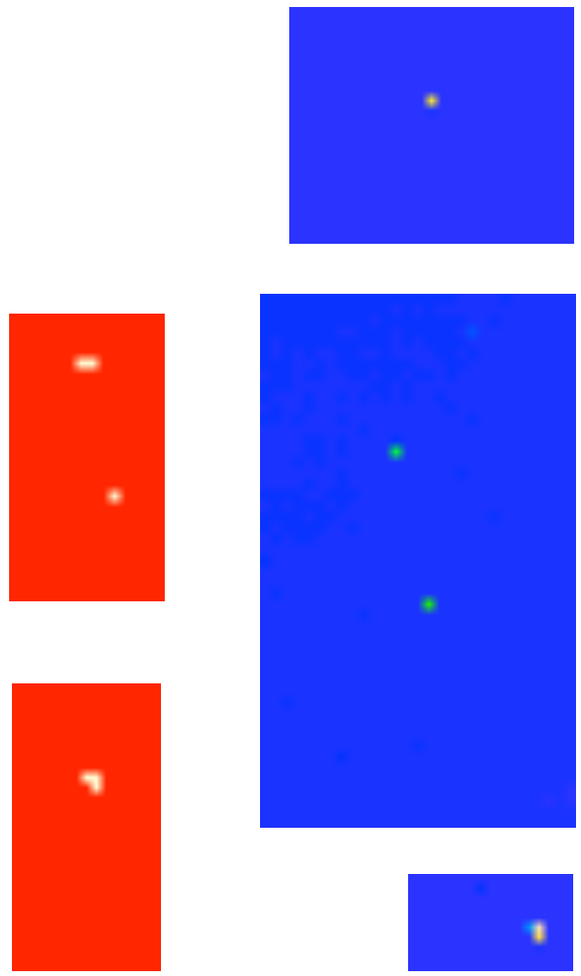
Readout groups (ROG):
Upper groups transferred first, starting read out from the upper row.
Lower groups starting from the last row.

Local defects: Isolated dead pixels

Singles, doubles, small clusters



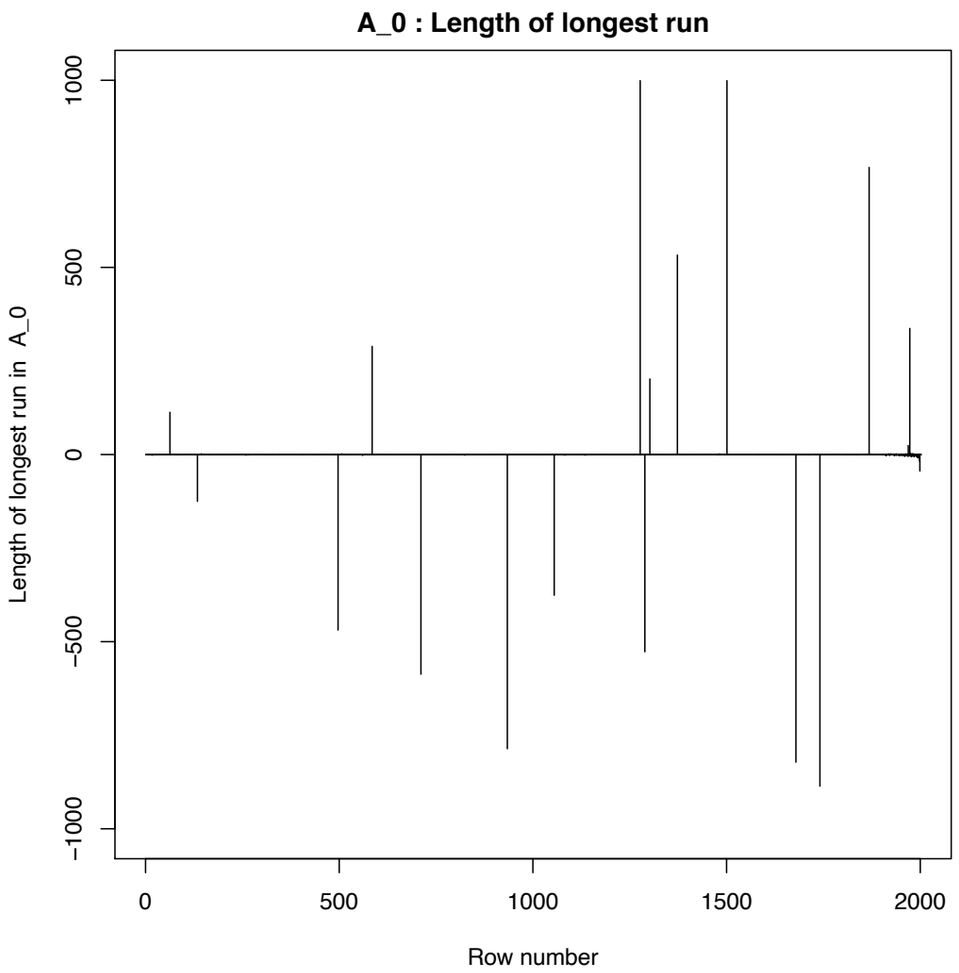
A_0: Grey image [R]



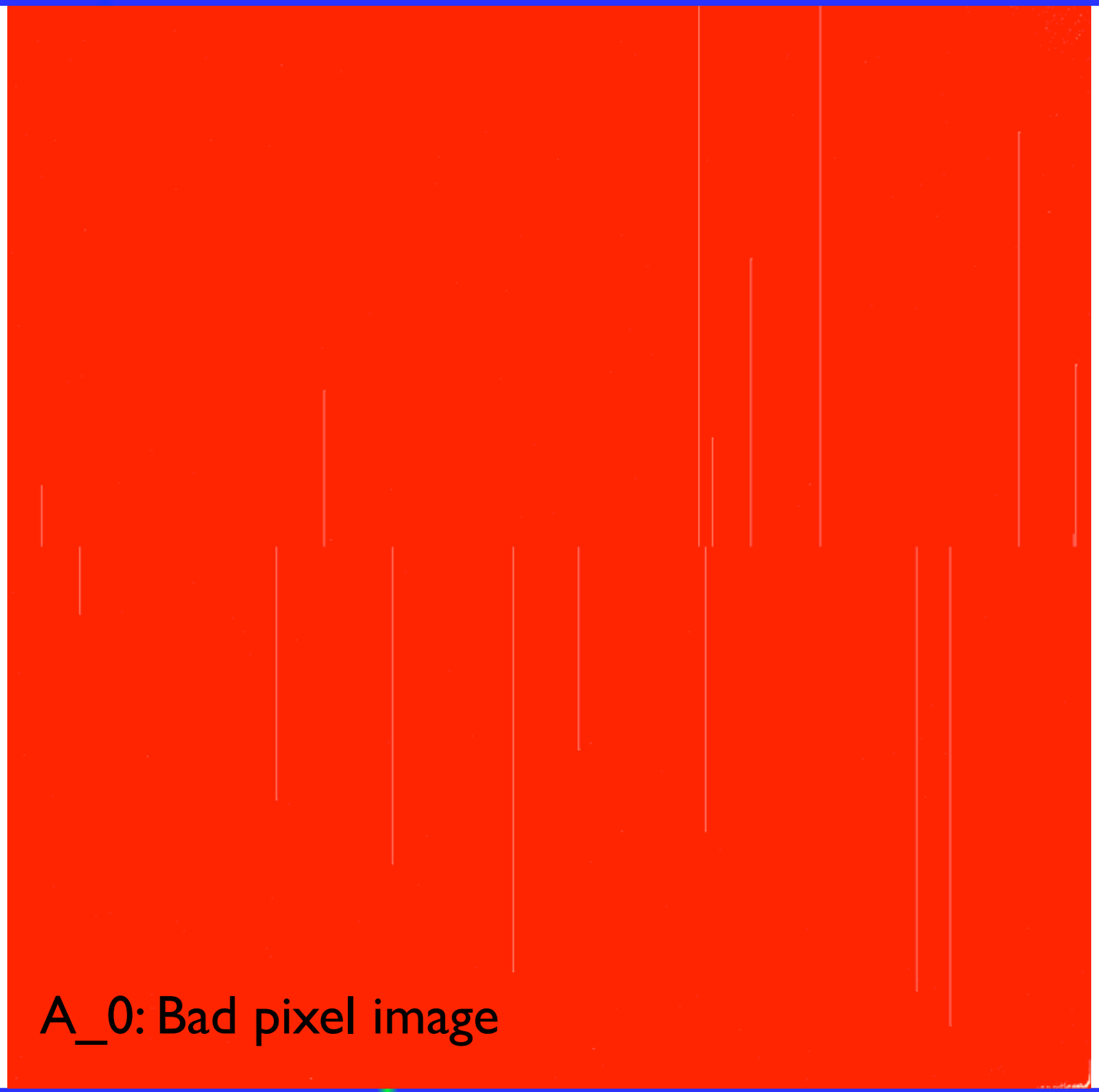
A_0:
bp binary
image [R]

A_0: Black
image [R]

Local defects: Dead lines



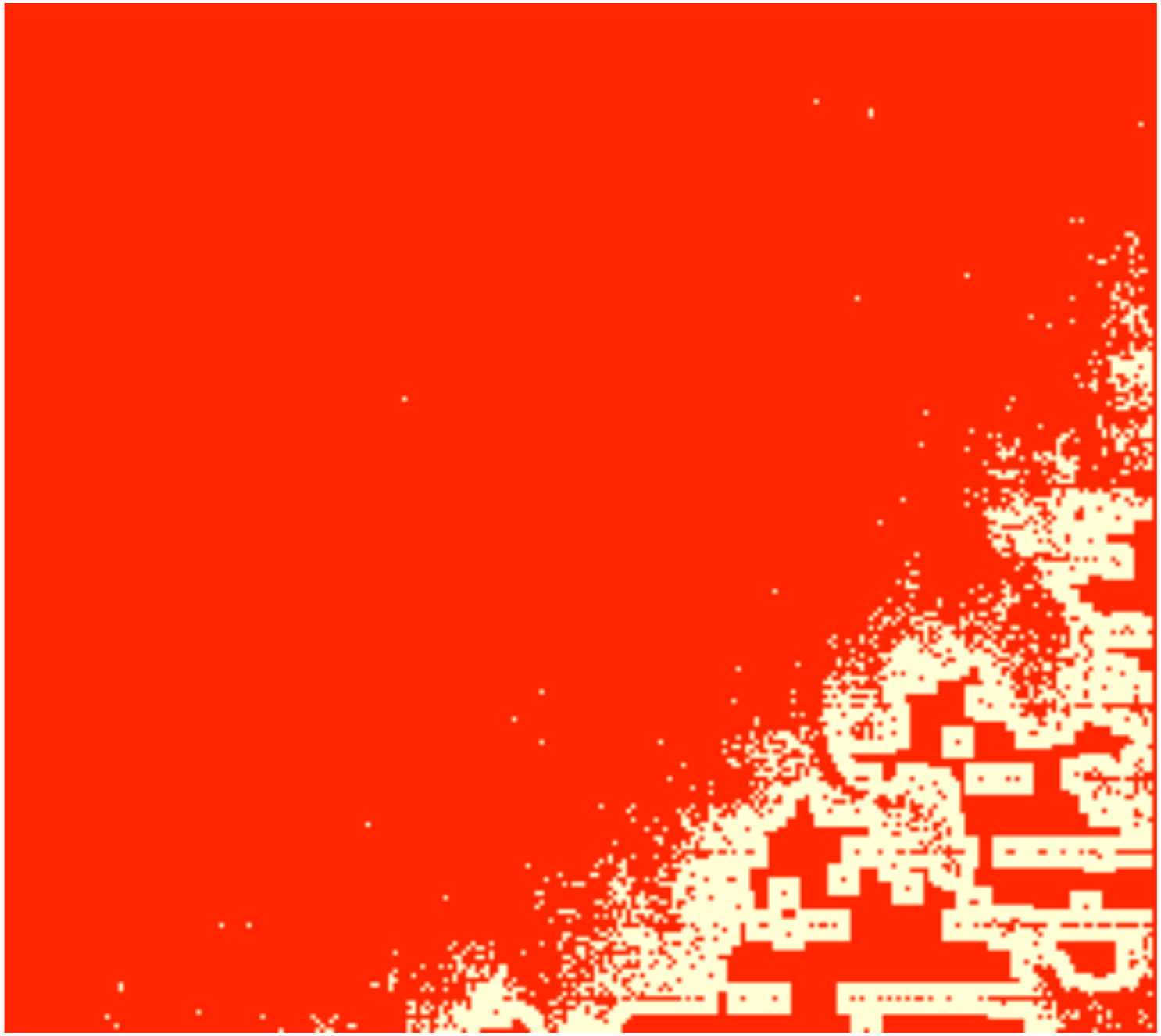
A_0: Graph of bad pixel images



A_0: Bad pixel image

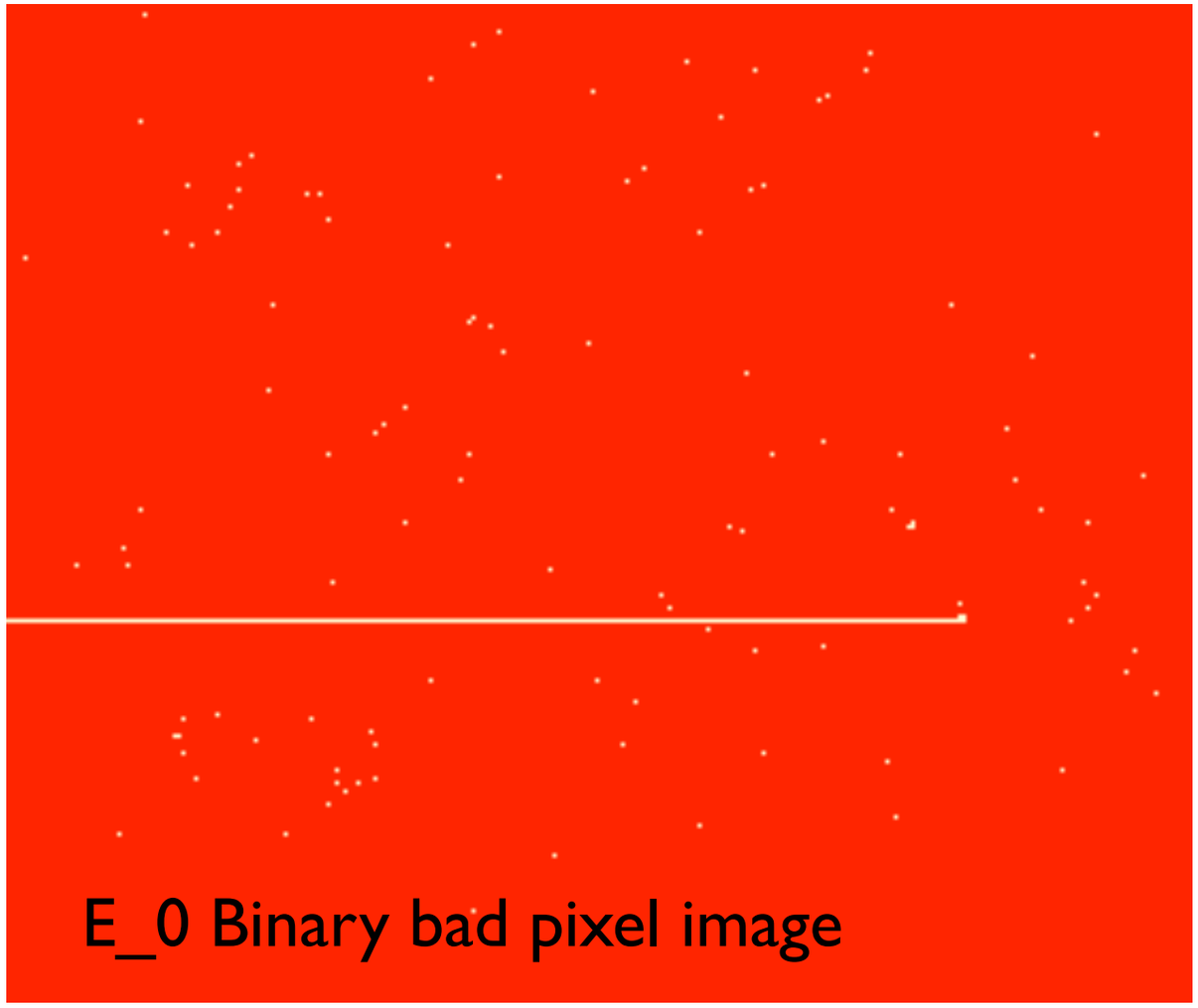
Local defects: Corners

B_0: Binary bad pixel image [R]

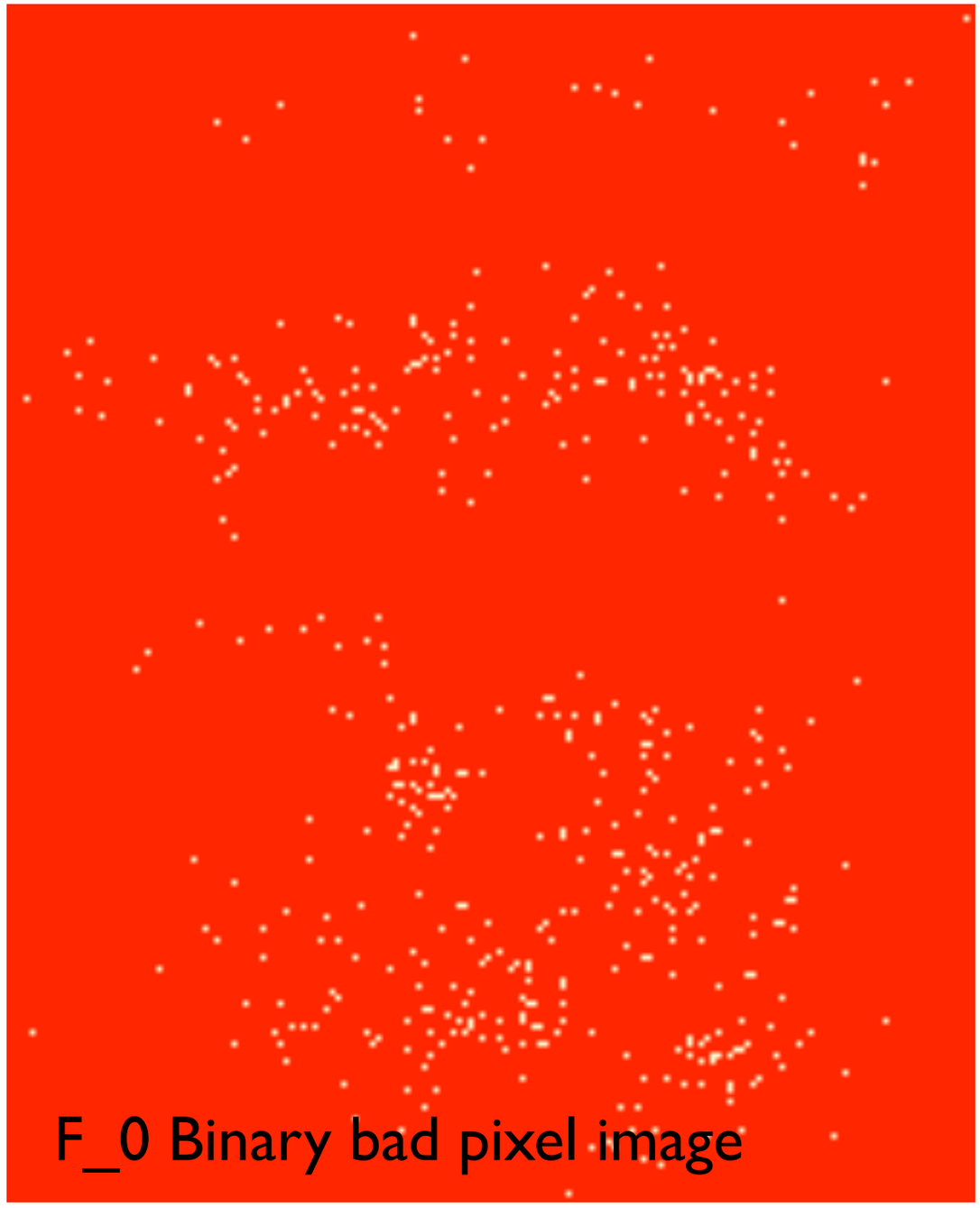


Local defects: Patches

- Areas with high density area of bad pixels



E_0 Binary bad pixel image



F_0 Binary bad pixel image

Spatial model for dead pixels

Dead pixel set as point process

Detector is based on a lattice, but ***our interest*** is in ***locations*** *of dead pixels and these are relatively few.* Hence, use a *spatial point pattern* model, but with reduced resolution (given by the detector lattice).

Point pattern X: random locations of dead pixels (2 dimensional)

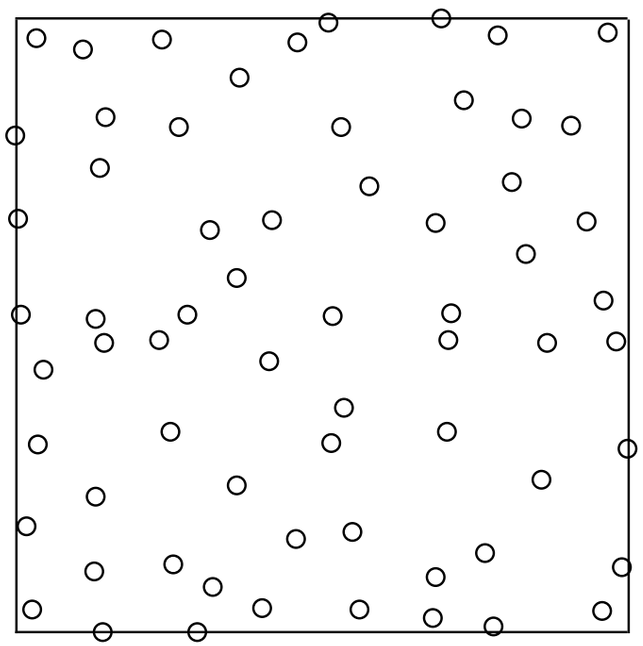
Objectives:

- describe spatial distribution of dead pixels
- hypothesise causes for dead pixels

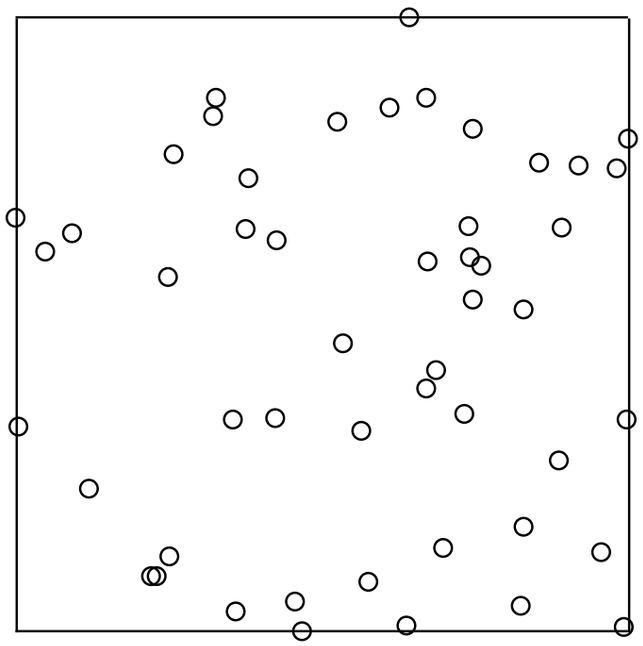
For example, look at CSR…

Complete spatial randomness (CSR)

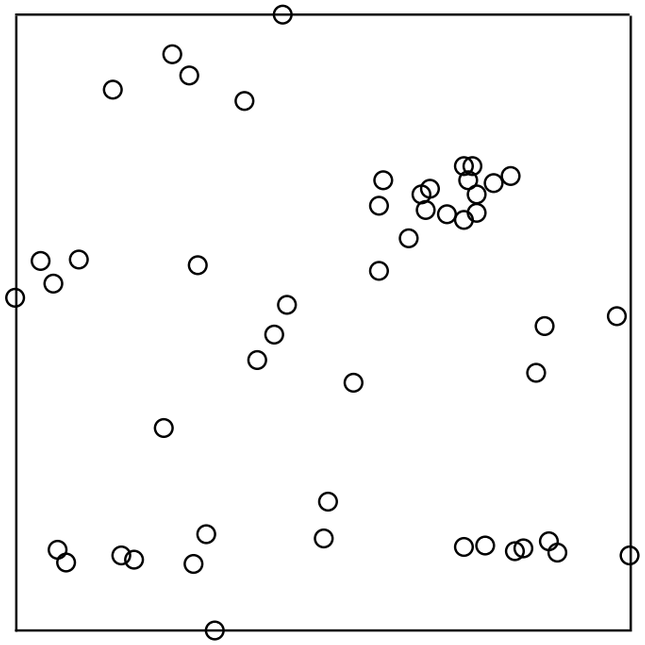
CSR: Points are distributed independently and homogeneously, as in a homogenous Poisson process.



Regular (nearly)



CSR



Clustering

Exploring CSR using F- and G-functions

Nearest neighbour function G:
Cumulative distribution function of the distance from an arbitrary point to its nearest point

Under CSR: $G(r) = 1 - \exp(-\lambda \pi r^2)$

Empty space function F:
Cumulative distribution function of the distance from an arbitrary location to its nearest point

Under CSR: $F(r) = 1 - \exp(-\lambda \pi r^2)$

Exploring CSR using Ripley's K-function

K-function:
expected number of extra points in circle of radius r rescaled by density

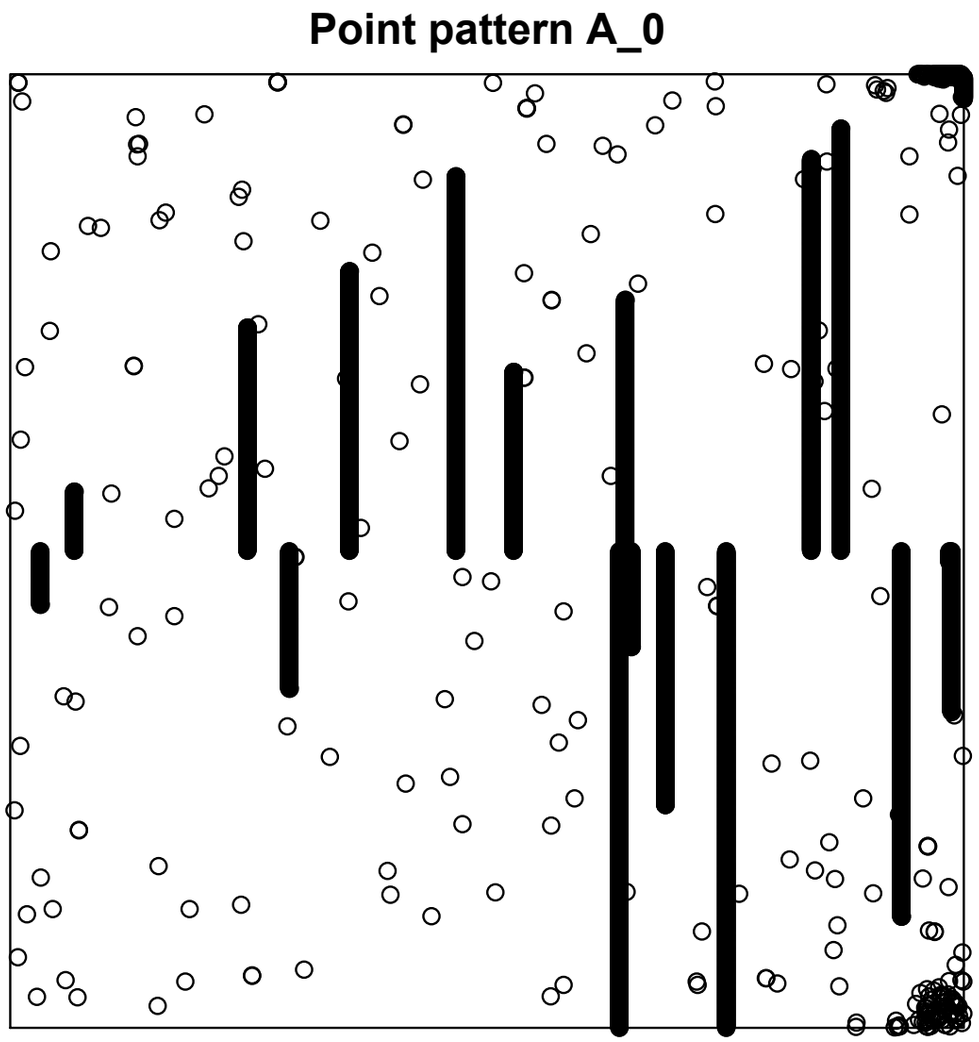
$$K(r) = \lambda^{-1} E[N_0(r)]$$

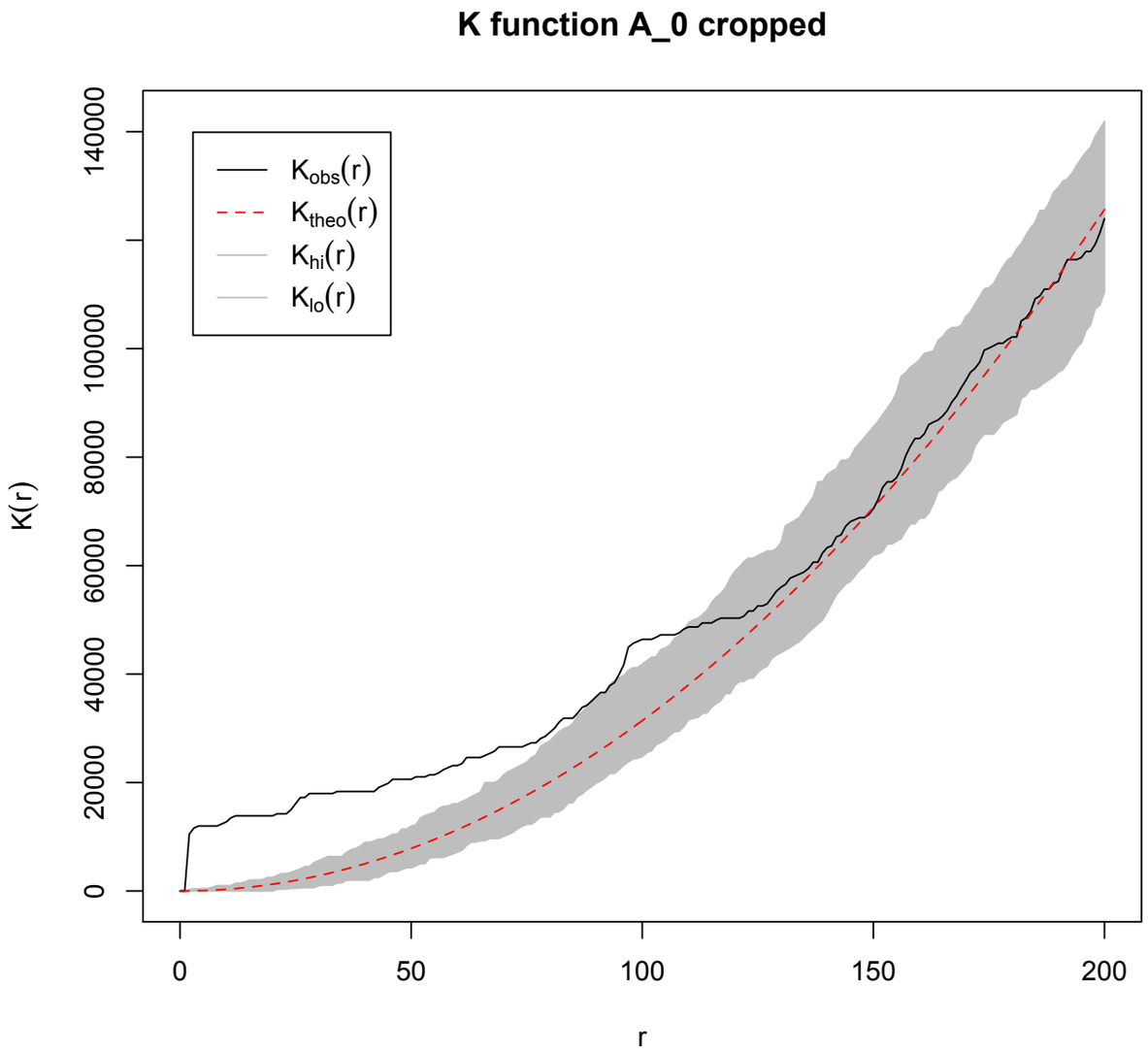
$N_0(r)$ number of points within distance r from arbitrary point

λ globally estimated density

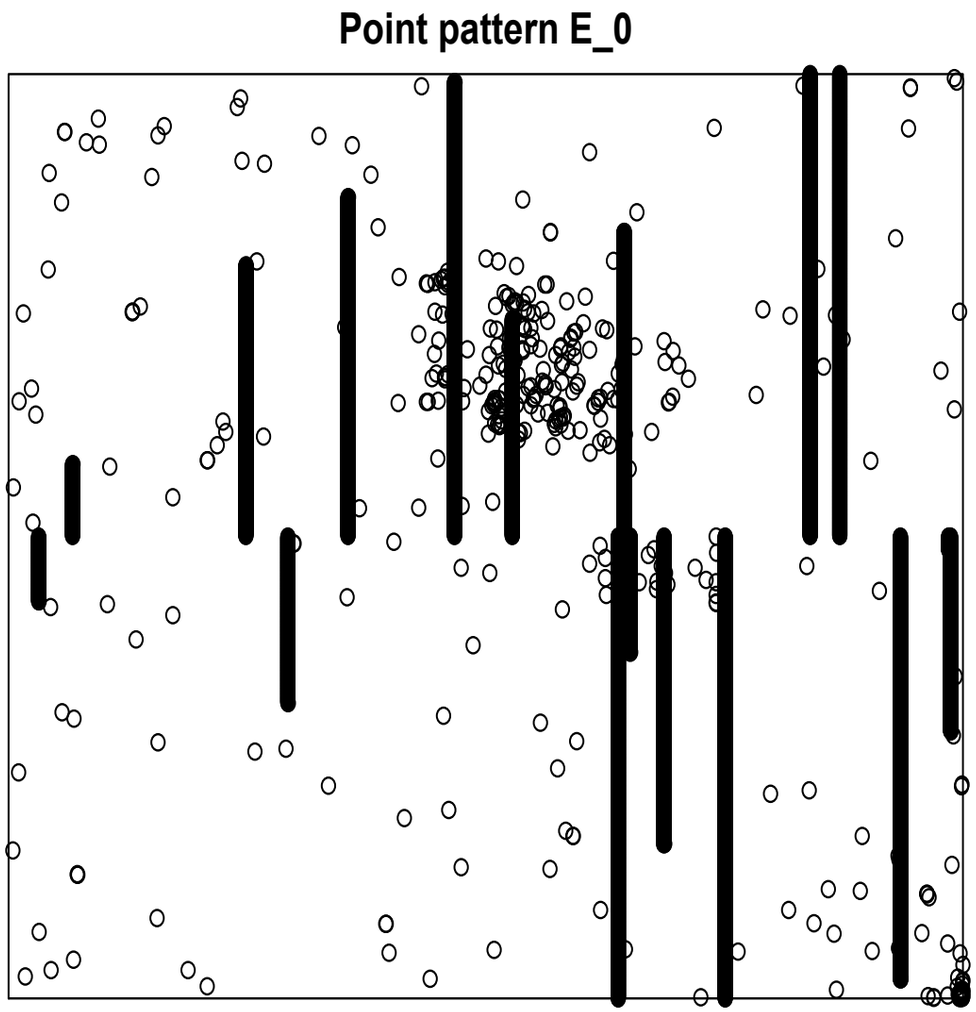
Under CSR: $K(r) = \pi r^2$

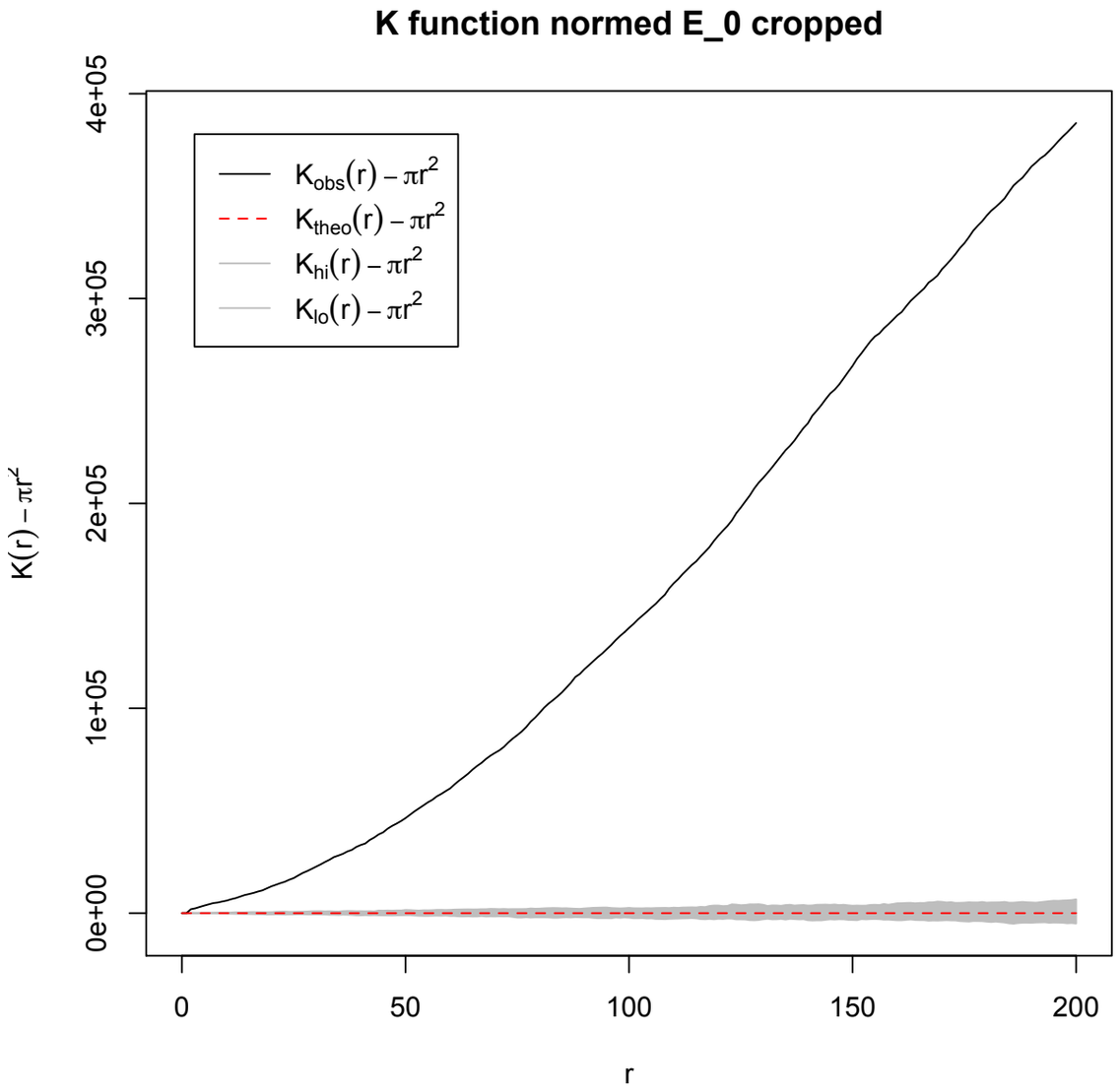
Point pattern and K-function





Point pattern and K-function





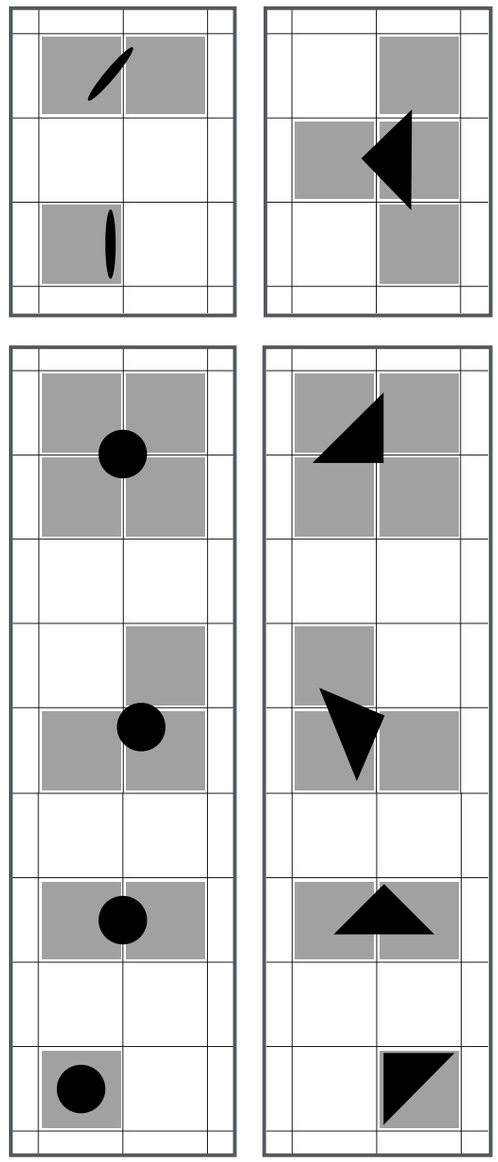
Are we asking the right question?

Modified question: Is it CSR after we remove all specific (known) problems?

Step 1:

Convert point process into *event process* by

- Reducing a line to one endpoint
- Reducing a clusters to its centre point

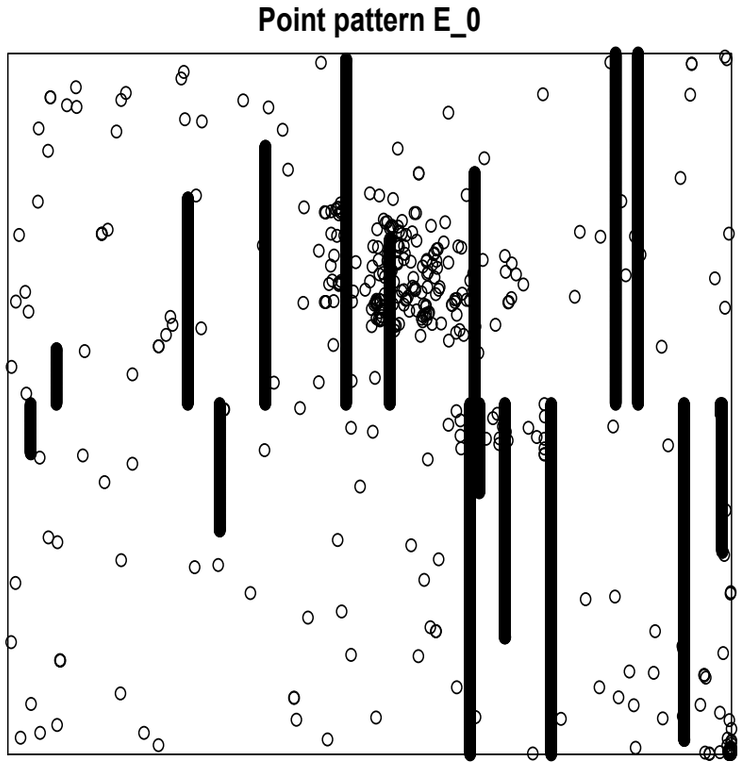


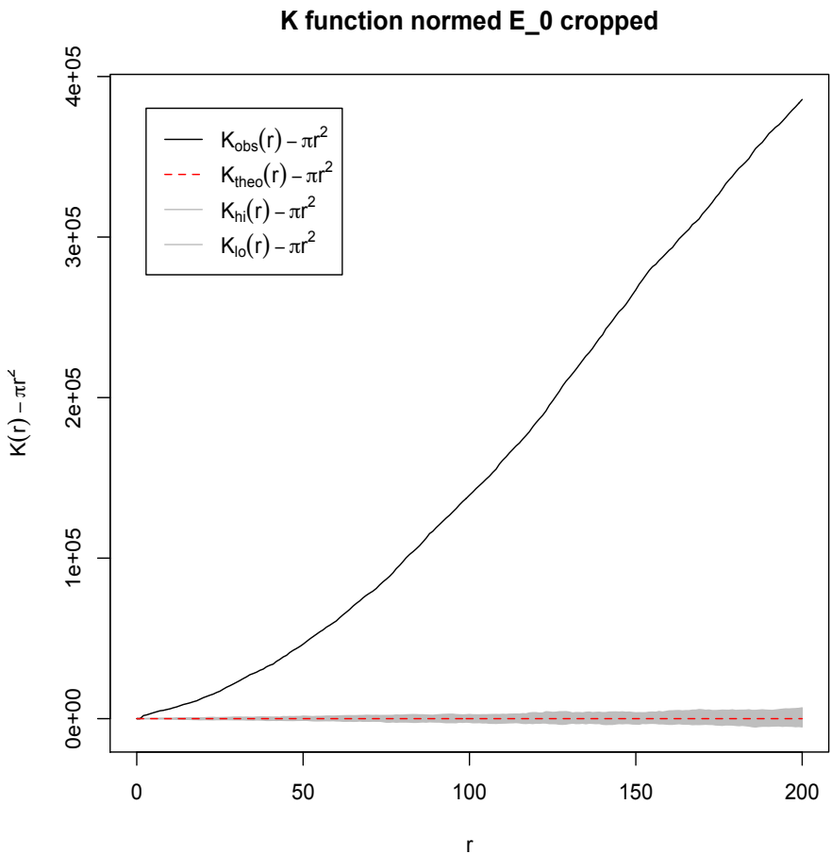
Step 2:

- Fit inhomogeneous density
- Cut out areas above threshold

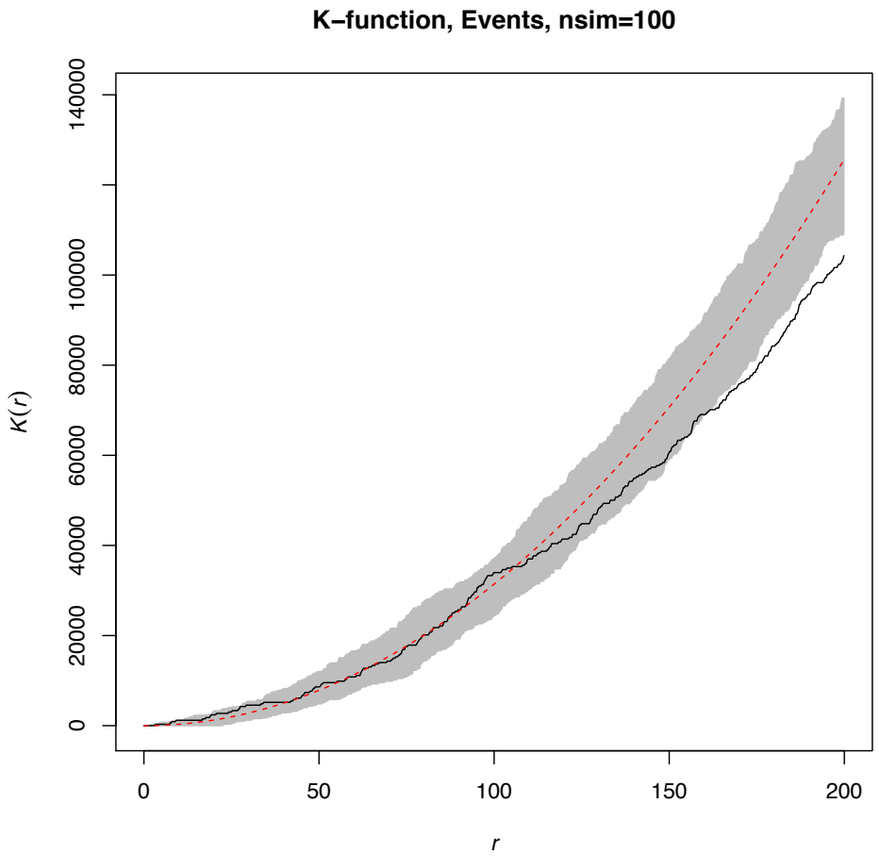
Modified process: K-function

Pixel level





Event level



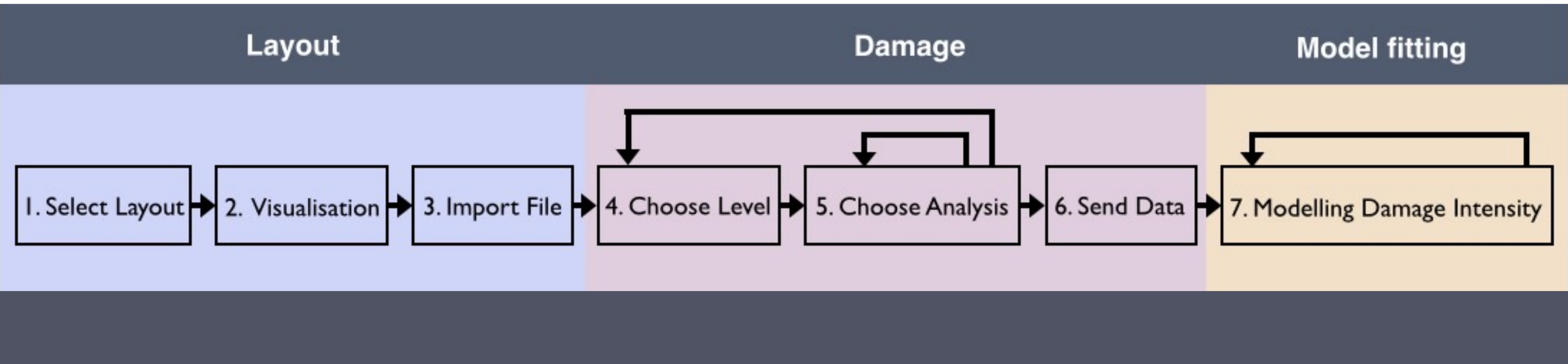
Not CSR

CSR

Seed funding for a software project with Turing

- Working with Turing Research Software Engineer Group
- *DetectorChecker* R package for statistical analysis of pixel damage in CT scanners available at https://github.com/alan-turing-institute/DetectorChecker
- *DetectorCheckerWebApp* for useful initial graphical/analysis, available at https://detectorchecker.azurewebsites.net
- Facility to upload data in different formats (crowd sourcing)

Brettschneider, Giles, Kendall, Lausaskas, (2020). DetectorChecker: analyzing patterns of defects in detector screens. Journal of Open Source Software, 5(56), 2474

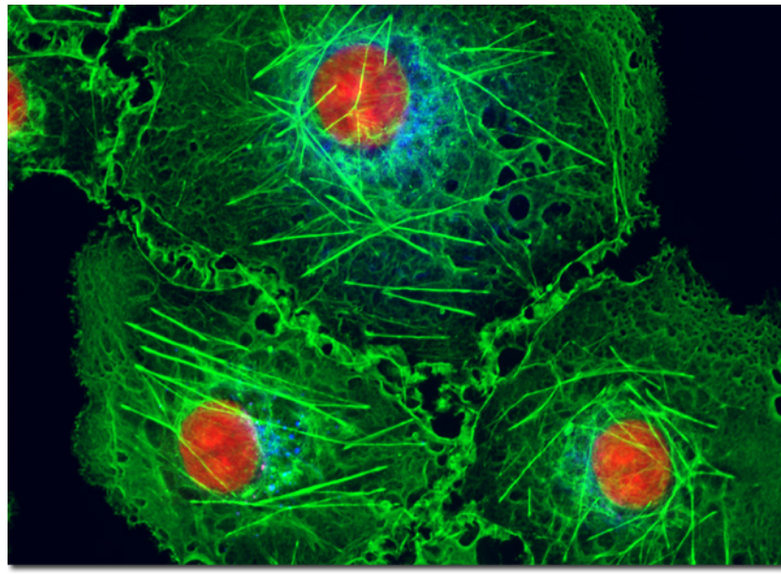


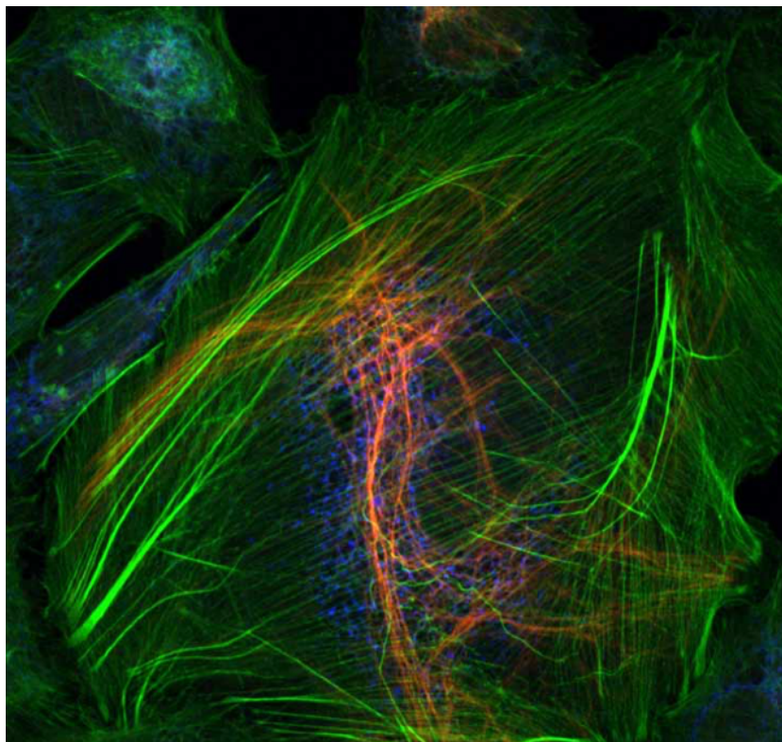
Microscopic image based modelling of biological processes

Quantifying spatial abundance of proteins in living cells

Confocal fluorescent laster microscopy (live cells)

Electron microscopy (dead cells, higher resolution)





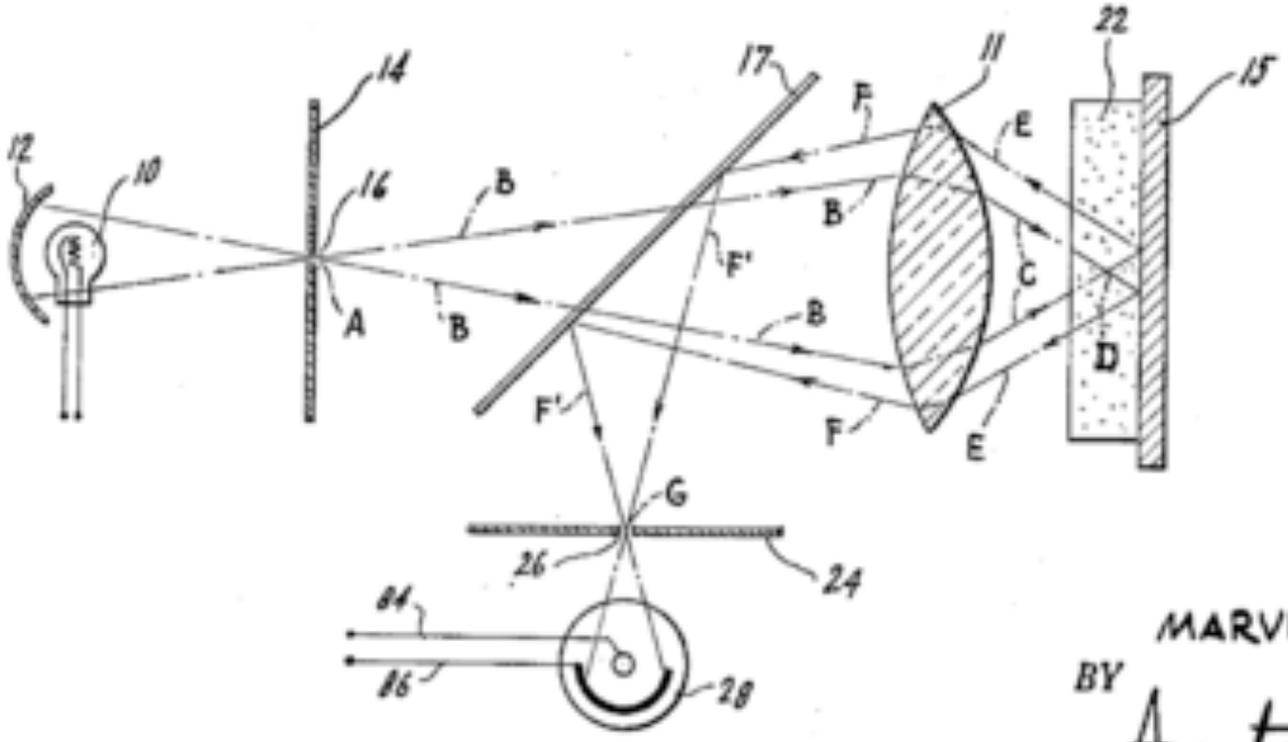


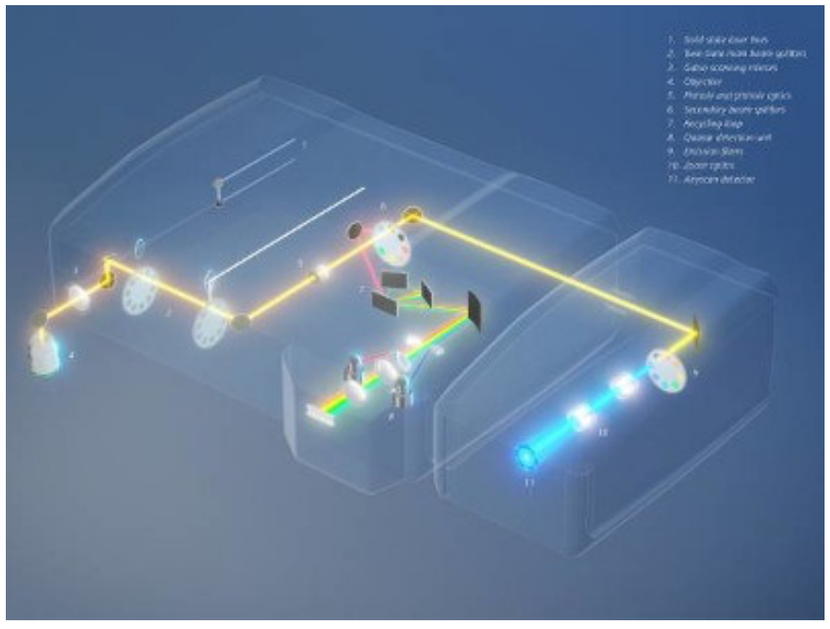
FIG. 3.

INVENTOR.
MARVIN MINSKY
BY
Ameter & Levy
ATTORNEYS

Confocal fluorescent laser microscope

Fluorescent confocal microscope:

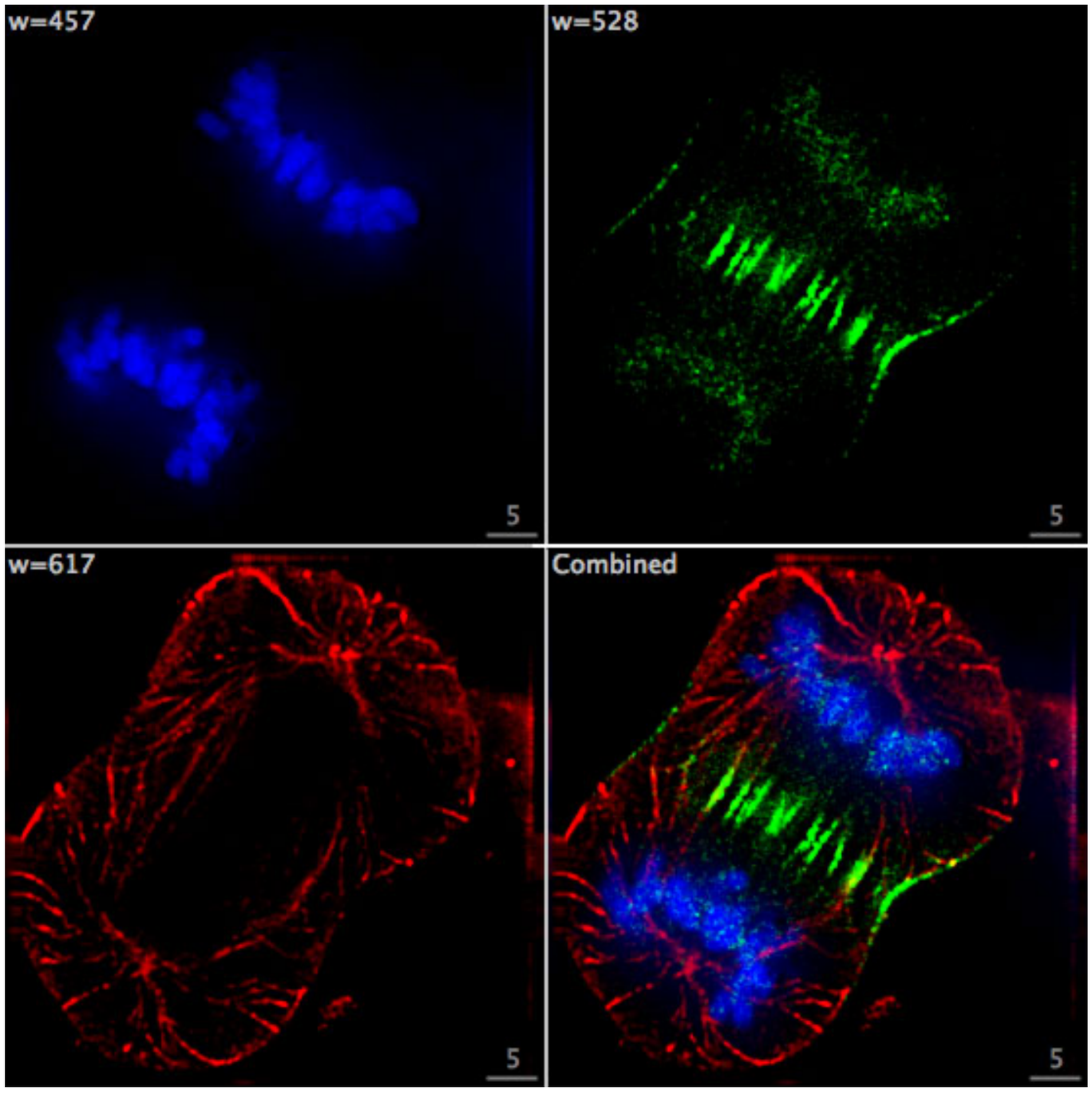
- Combination of two ideas in microscopy technology
- High resolution images
- Life cells
- 2D or 3D through scanning schemes
- Multi-channel through use of range of fluorescent proteins



https://www.biocompare.com/25608-Microscopes-and-Cell-Imaging-Systems/14617250-ZEISS-LSM-980-Confocal-Laser-Scanning-Microscope/?pda=25608|14617250_0_1|2254289,2254327|1|&dfp=true

https://en.wikipedia.org/wiki/Green_fluorescent_protein#/media/File:Fluorescence_from_Fluorescent_Proteins.jpg

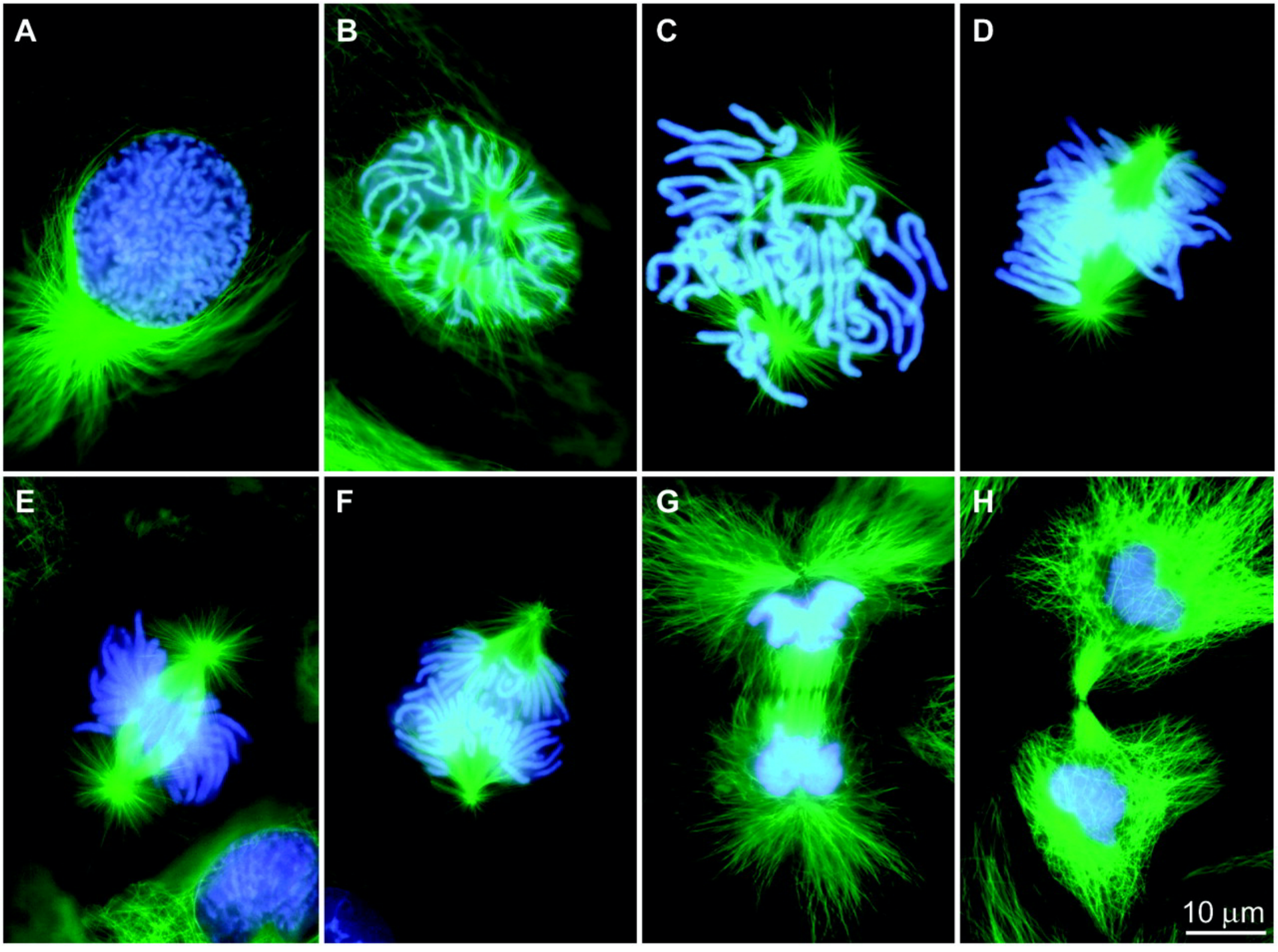
Example:
3 components in dividing human cancer cells



Scanning scheme for fluorescent imaging:

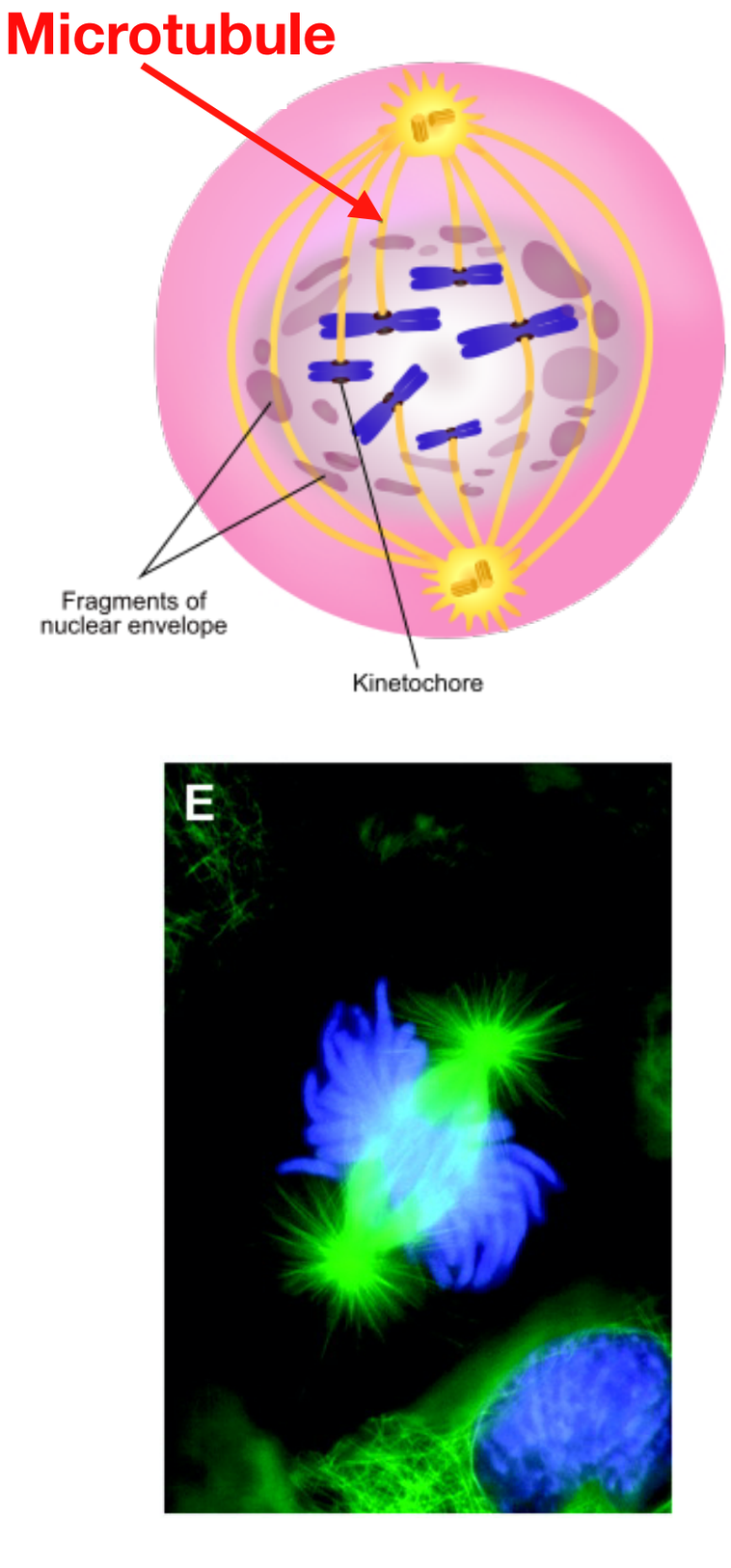
- Blue: Chromosomes (DNA)
- Green: INCENP (protein)
- Red: microtubules
- Fluorophores imaged separately using different excitation and emission filters
- Images captured sequentially
- Overlaid

Microtubules formation during mitosis



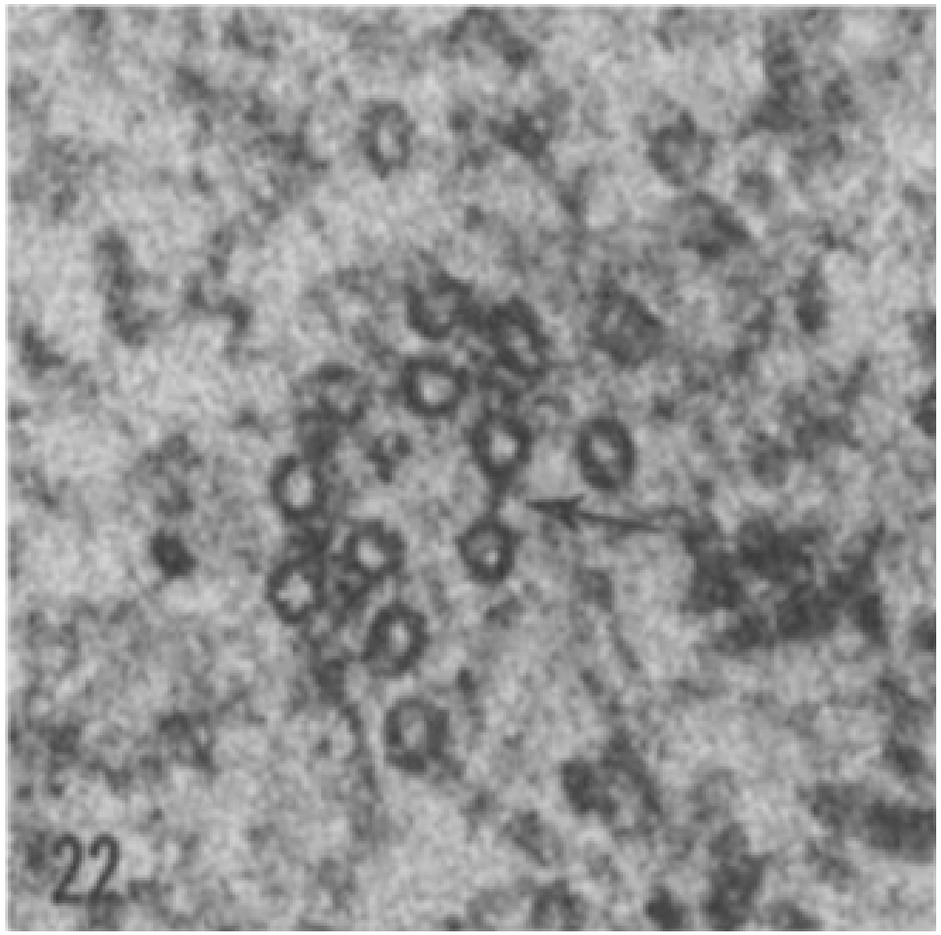
https://science.sciencemag.org/content/300/5616/91/tab-figures-data

Microtubules during mitosis (cell division)

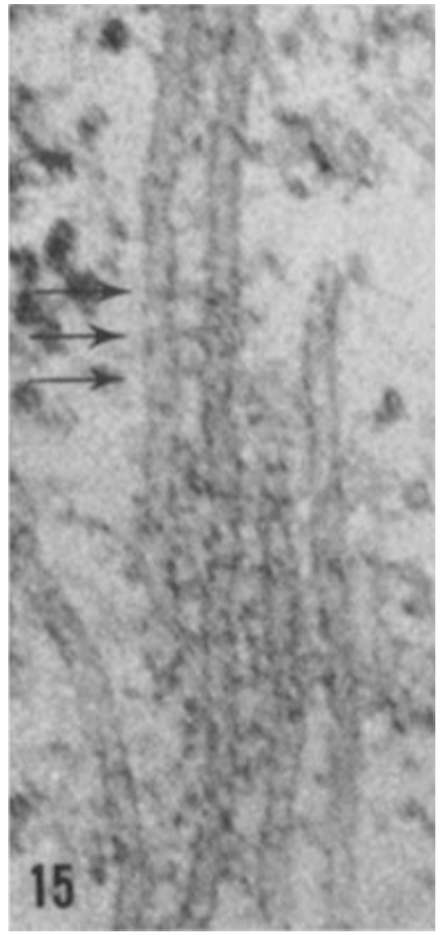


- Centrosomes = centrioles + microtubules
- Centrioles help the spindle into proper formation
- Spindle microtubules are arranged in K-fibers
- Intertubule bridges formed by mesh

Perpendicular to the microtubule axis



Parallel



https://www.scienceabc.com/nature/mitosis-vs-meiosis-how-does-cell-division-work.html

Microtubules locations as point patterns

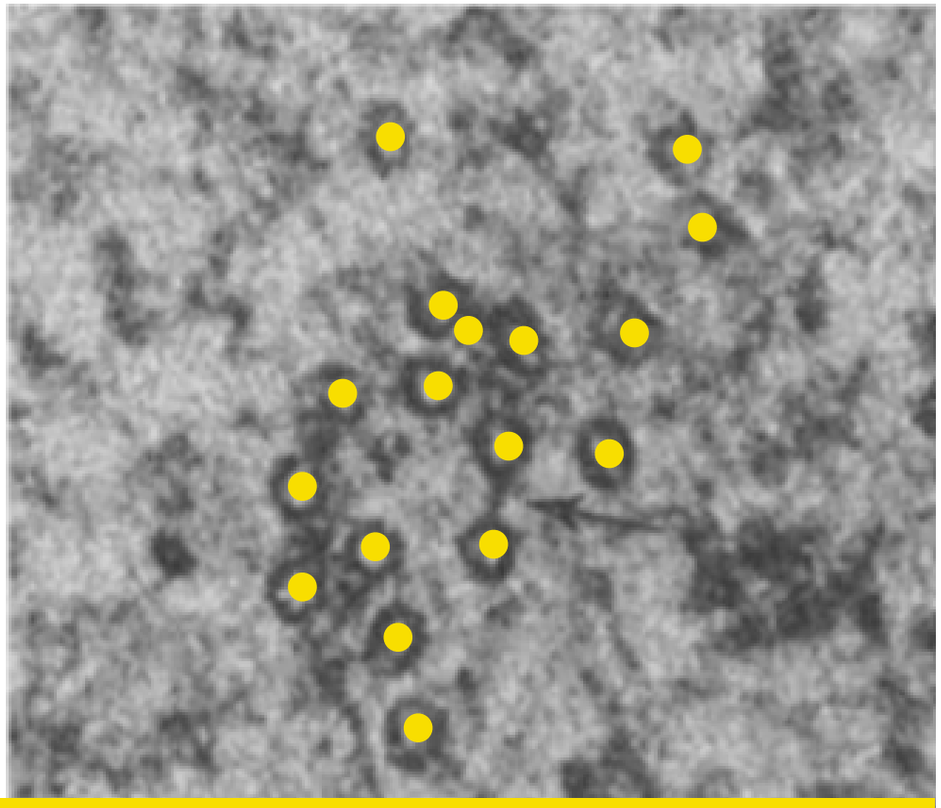
Stephen Royle's Lab (Centre for Mechanochemical Cell Biology) asks:
What is the role of TACC3 protein for the structure of microtubules within K-fibres and mesh?

Experiment: Overexpression of TACC3 through treatment versus control.

Data: Microscopic images collected in planes perpendicular to the fibre axes.

Team:
Steve Royle
Tom Honnor (now at UCL)
Adam Johnson
Julia Brettschneider

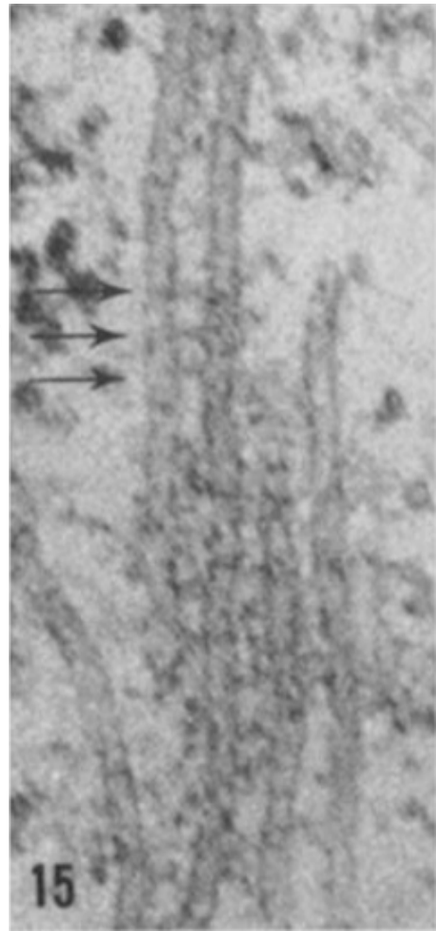
Perpendicular view



Model: locations as point pattern

Parallel

Mesh

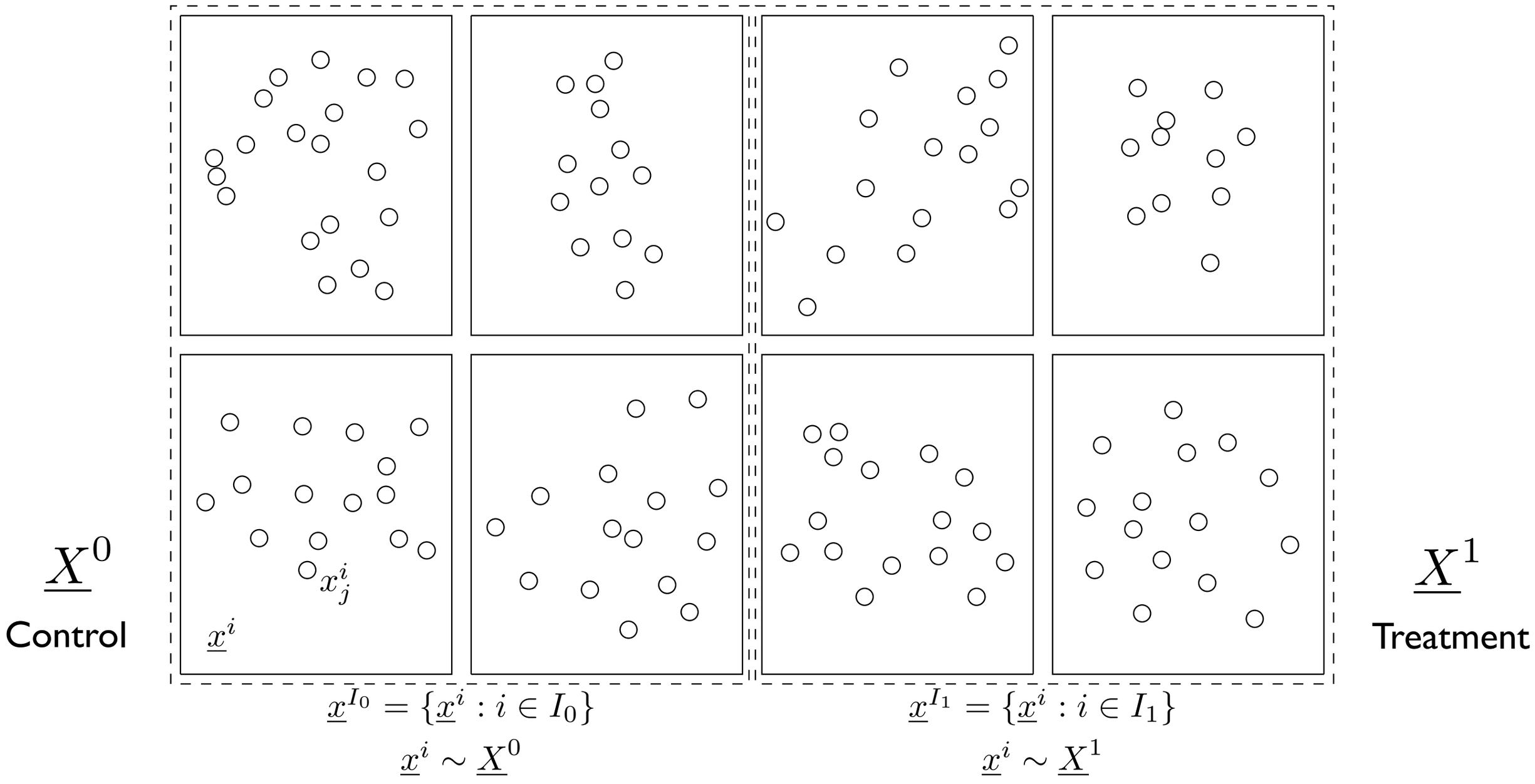


Study I: Microtubules - mathematical model

Data:

Microscopic images of treatment (n=37) versus control (n=26)

Observation window surrogate for cross sectional area of K-fibres



Point patterns models

Set of point patterns:

$$\chi_2 := \{(\underline{x} = x_1, x_2, \ldots, x_{n(\underline{x})}) : n(\underline{x}) \in \mathbb{N}, x_i \in \mathbb{R}^2 \text{ for } i = 1, 2, \ldots, n\}$$

Model pattern as realisations of a point process:

Random subset $\underline{X}$ on $\mathbb{R}^2$.

For B in Borel σ-algebra $\mathcal{B}(\mathbb{R}^2)$ on $\mathbb{R}^2$: $\underline{X}_B = \underline{X} \cap B$

Counts (random variable): $N(B) = n(\underline{X}_B) =$ number of points of $\underline{X}$ in B

Intensity measure μ

$$\mu(B) = \mathbb{E}[N(B)], \quad \forall B \in \mathcal{B}(\mathbb{R}^d).$$

If for some function $\rho : \mathbb{R}^2 \to [0, \infty)$

$$\mu(B) = \int_{x \in B} \rho(x) dx, \quad \forall B \in \mathcal{B}(\mathbb{R}^d),$$

then ρ is referred to as the intensity function of $\underline{X}$.

Summary statistics: basics

Let $\underline{x}$ be a realisation of $\underline{X}$ on the observation window W.

Estimator for the **intensity** of $\underline{X}$:

$$\hat{\rho} = \frac{n(\underline{x})}{|W|}$$

Let $\mathrm{nn}(x_j)$ be the (set of) nearest neighbours of point x_j.

$$\mathrm{nn}(x_j) = \{x_k : k = \mathrm{argmin}_l ||x_l - x_j||\},$$

and $\mathrm{nnd}(x_j)$ its nearest neighbour distance

$$\mathrm{nnd}(x_j) = \inf_{x \in \mathrm{nn}(x_j)} \{||x_j - x||\}.$$

Estimator for the **mean nearest neighbour distance** for $\underline{X}$:

$$\overline{\mathrm{nnd}}(\underline{x}) = \frac{1}{n(\underline{x})} \sum_{j=1}^{n(\underline{x})} \mathrm{nnd}(x_j)$$

Summary statistics: K-function

K-function (Ripley 1977) (scaled neighbourhood count function):

$$K(r) = \frac{1}{\rho}\mathbb{E}\left[\frac{1}{N(S)}\sum_{x_j \neq x_k \in \underline{X}} 1_{\{||x_j - x_k|| < r\}}\right]$$

Estimate:

$$\hat{K}(\underline{x}, r) = \frac{|W|}{n(\underline{x})^2}\sum_{j \neq k} e_{j,k} 1_{\{||x_j - x_k|| \leq r\}}$$

where $e_{j,k}$ is the proportion of the circumference of the circle with centre x_j and radius $||x_j - x_k||$ in W (edge correction).

$K(r) = \pi r^2$: CSR (complete spatial randomness)

$K(r) > \pi r^2$: aggregation at distances less than r

$K(r) < \pi r^2$: repulsion at distances less than r

Summary statistics: G-function

Nearest neighbour function (Diggle 2003):

$$G(r) = \frac{1}{\rho|B|}\mathbb{E}\left[\sum_{x\in \underline{X}_B} 1_{\{\underline{X}\setminus x)\cap b(x,r)\neq 0\}}\right]$$

for finite B in $\mathbb{R}^2$, and $b(x,r)$ the disc centred at x with radius r.
(For stationary $\underline{X}$ it is independent of B.)

Distribution of distance of randomly selected point to its nearest neighbour.

Estimate:

$$\hat{G}(\underline{x},r) = \frac{1}{n(\underline{x})}\sum_{j=1}^{n(\underline{x})} 1_{\{\mathrm{nnd}(x_j)\leq r\}}$$

If $\underline{X}$ is completely spatially at random then $G(r) = 1-\exp(-\rho\pi r^2)$

Test statistics based on basic observations

Pattern size test statistic:

$$\delta_N(I) = \frac{1}{|I_0|}\sum_{i\in I_0} n(\underline{x}^i) - \frac{1}{|I_1|}\sum_{i\in I_1} n(\underline{x}^i)$$

Observation window statistic:

$$\delta_W(I) = \frac{1}{|I_0|}\sum_{i\in I_0} |W^i| - \frac{1}{|I_1|}\sum_{i\in I_1} |W^i|$$

Intensity test statistic:

$$\sum_{i\in I_0} \omega_0(\underline{x}^i)\hat{\rho}(\underline{x}^i) - \sum_{i\in I_1} \omega_1(\underline{x}^i)\hat{\rho}(\underline{x}^i)$$

where $\delta_\rho(I)$ denotes unweighted case using $\omega_k(\underline{x}^i) = 1/|I_k|$ $(k = 0, 1)$

$\delta_{\rho,\omega}(I)$ denotes weighted case using $\omega_k(\underline{x}^i) = n(\underline{x}^i) \Big/ \sum_{j\in I_k} n(\underline{x}^j)$ $(k = 0, 1)$

Test statistics based on G-functions

Estimated nearest neighbour functions averaged
over the collection of point patterns $\underline{x}^J$ with weights ω_J as above:

$$\hat{G}(\underline{x}^J, r) = \sum_{i \in J} \omega_J(\underline{x}^i) \hat{G}(\underline{x}^i, r)$$

Nearest neighbour distribution test statistic statistics:

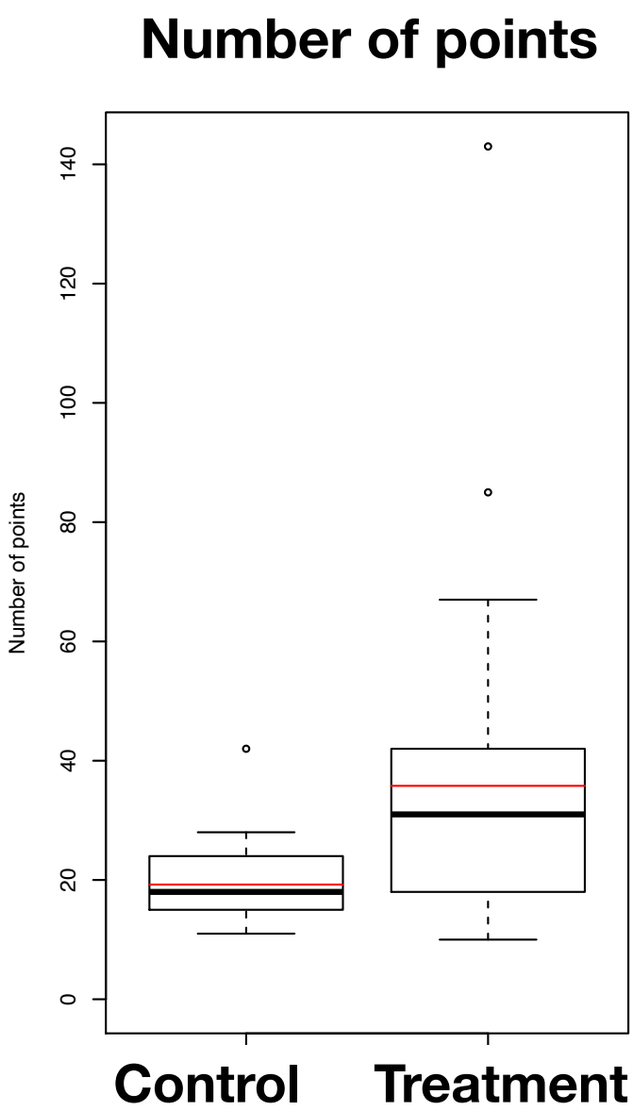
$$\delta_{G,1}(I) = ||\hat{G}(\underline{x}^{I_0}, r) - \hat{G}(\underline{x}^{I_1}, r)||_1 = \int_0^\infty |\hat{G}(\underline{x}^{I_0}, r) - \hat{G}(\underline{x}^{I_1}, r)| dr$$

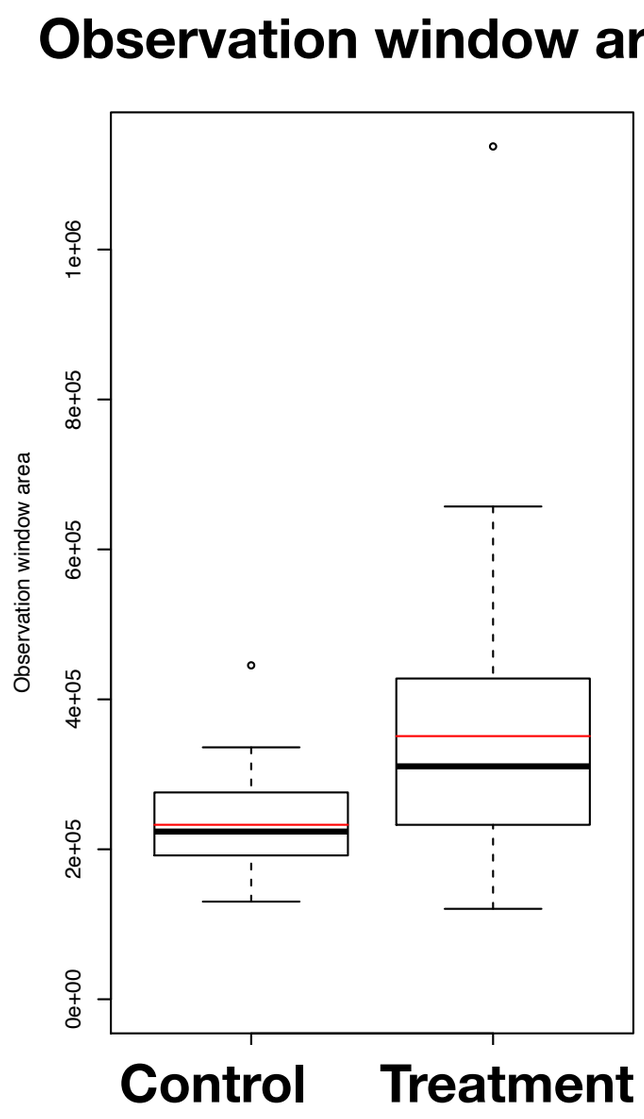
$$\delta_{G,\infty}(I) = ||\hat{G}(\underline{x}^{I_0}, r) - \hat{G}(\underline{x}^{(I_1}, r)||_\infty = \sup_r |\hat{G}(\underline{x}^{I_0}, r) - \hat{G}(\underline{x}^{I_1}, r)|$$

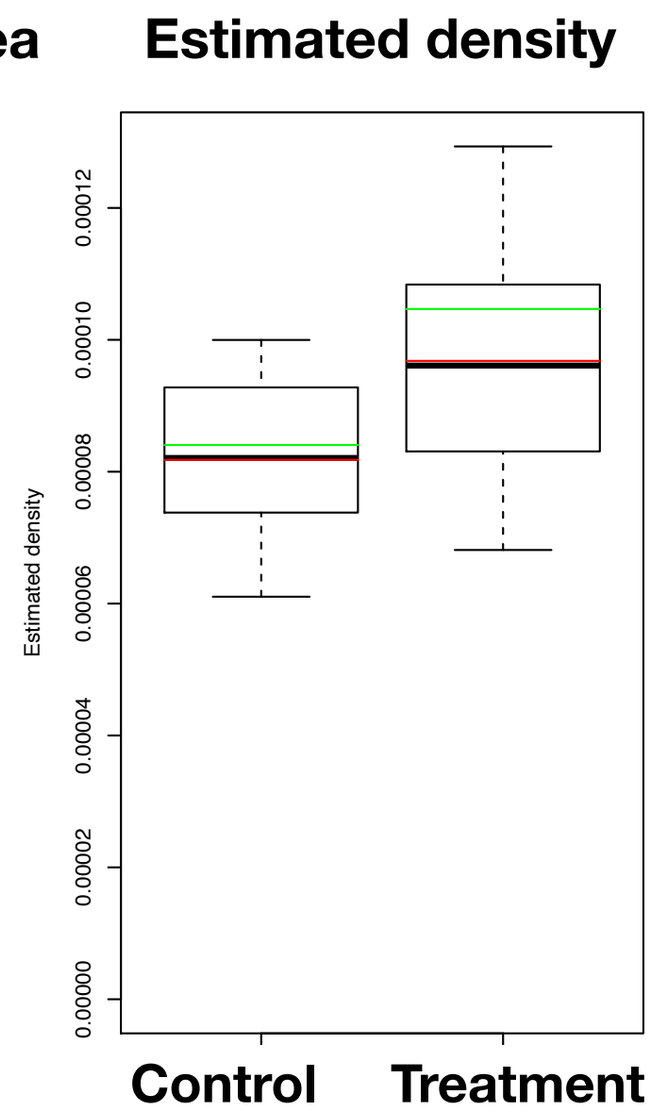
For comparison of $\hat{G}(\underline{x}^{I_0}, r)$ and $\hat{G}(\underline{x}^{I_1}, r)$
across the range of distances $r > 0$.

Also, scaled neighbourhood count test statistic (Diggle 2000).

EDA: First order statistics



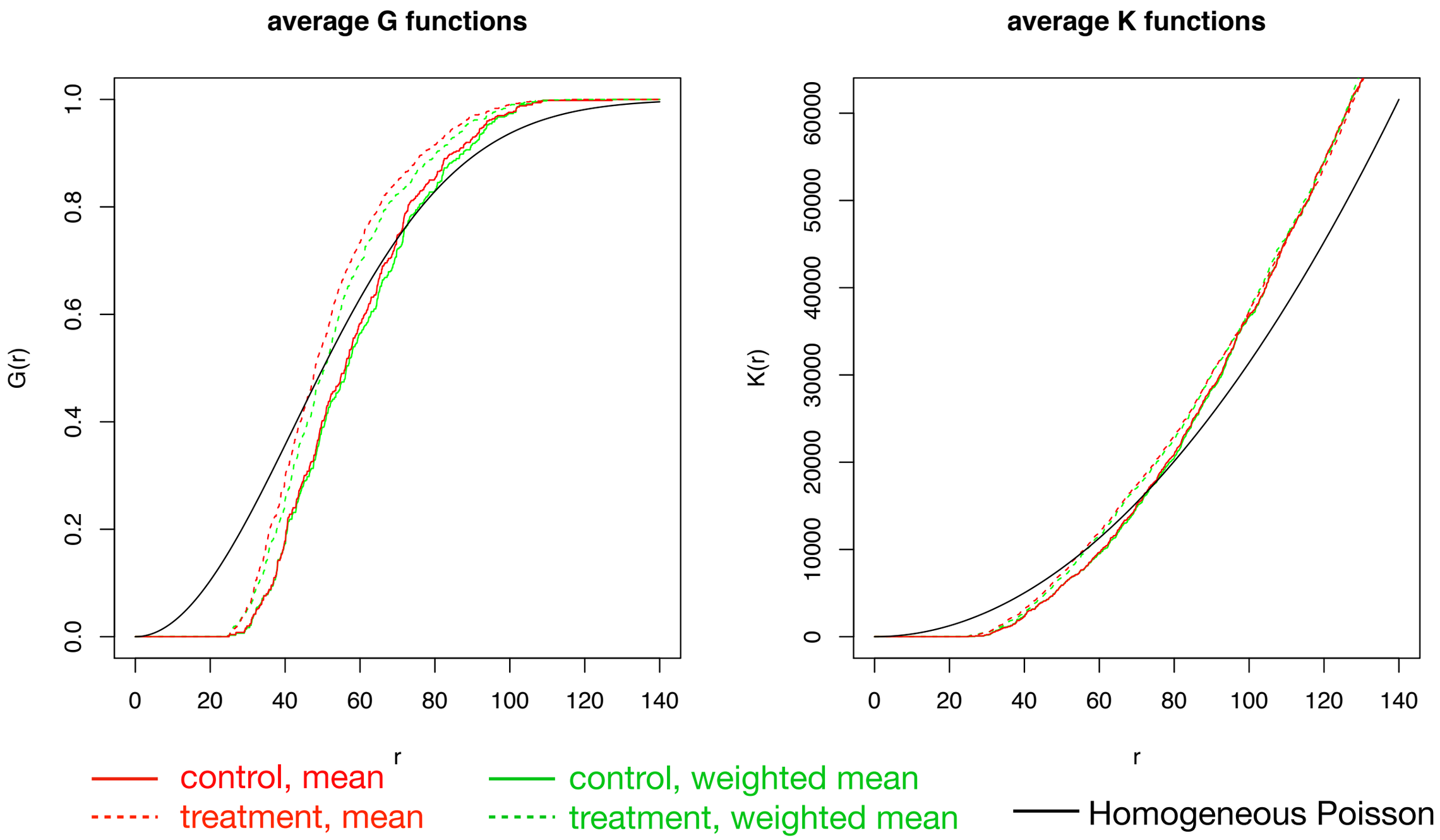




mean
weighted mean

- All means/medians are greater for treatment
- Treated K-fibers are made up of a greater number of microtubules which are more closely separated within thicker K-fibers
- Weighted mean densities greater than unweighted means densities (i.e. K-fibers with greater numbers of microtubules are more tightly packed

EDA: Spatial functions



- Some evidence of clustering at larger length scales
- Effect of limitation of nnd in [25,105]
- Difference between weighted mean and unweighted mean negligible

Significance quantification

- Based on permutation tests (nonparametric)
- Need exchangeability under the Null under suitable set of operations
- Statistics under permutations are identically distributed
- p-values are uniformly distributed (test e.g. with KS)
- Exact or approximate (subset of operations)
- Evaluated in simulations studies

Test statistics

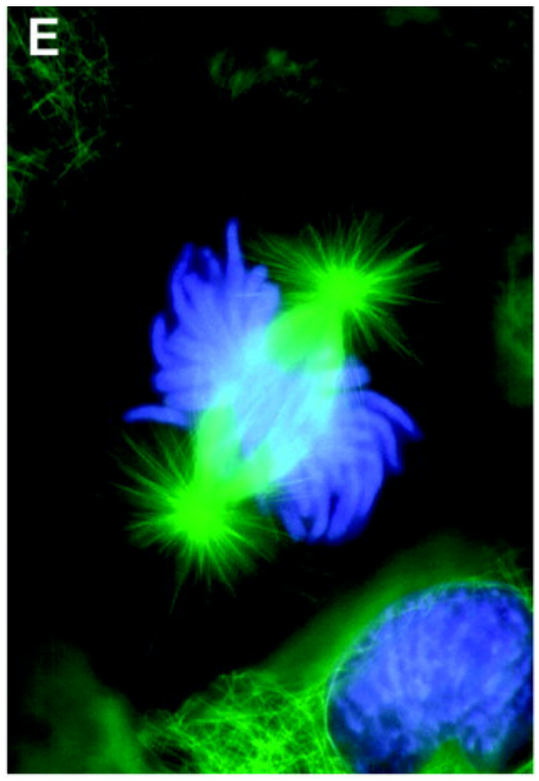
Observations of exploratory analysis can be confirmed by formal testing.
All proposed test statistics show significant results:

δ_N	0.0005	δ_{nnd}	0.0057	δ_K	0.1092	δ_{EFT}	0.0011
δ_W	0.0018	$\delta_{\text{nnd},\omega}$	0.0005	$\delta_{G,1}$	0.0061	$\delta_{EFT,\omega}$	0.0005
δ_ρ	0.0001	δ_{msd}	0.0019	$\delta_{G,1,\omega}$	0.0005		
$\delta_{\rho,\omega}$	0.0002	$\delta_{\text{msd},\omega}$	0.0005	$\delta_{G,\infty}$	0.0087		
				$\delta_{G,\infty,\omega}$	0.0013		

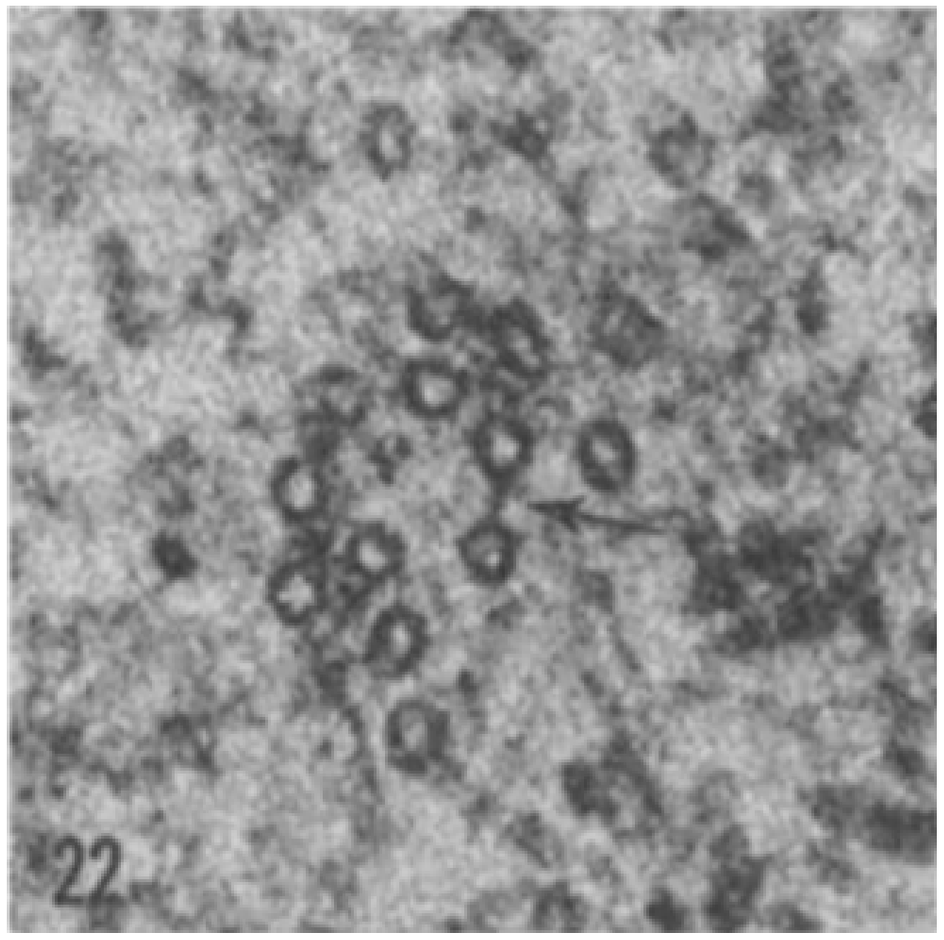
Results remain significant after multiple testing adjustment of critical p-value (using Bonferroni).

What did we find?

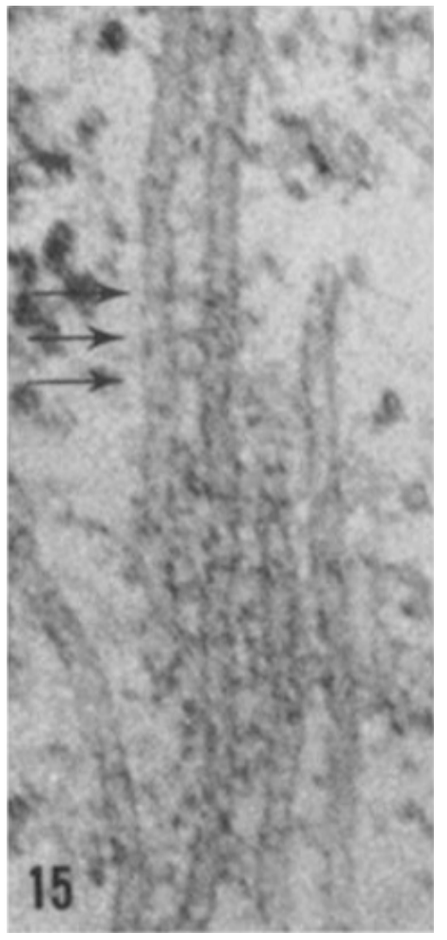
- Microtubules are **bound together** (in K-fibers, by mesh-like structure)
- TACC3 **overexpression** is **associated with an impact** on the mesh
- Detection of treatment effects not visible by eye



Perpendicular to the microtubule axis



Parallel view



References

The (ongoing) work on modelling Covid with Hawkes process is joint with Adam Davison and Marianna Mavroleftherou (integrated Masters students at Warwick Statistics)

Dead pixels and other work related to digital X-ray imaging:

JA Brettschneider, OT Giles, WS Kendall, T Lazauskas
DetectorChecker: analyzing patterns of defects in detector screens
Journal of Open Source Software, 2020, 5(56), 2474

JA Brettschneider, JW Warnett, TE Nichols, WS Kendall
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Kueh A, Warnett JM, Gibbons GJ, Brettschneider J, Nichols TE, Williams MA, & Kendall WS
Modelling the Penumbra in Computed Tomography
Journal of X-ray science and technology, 24 (4), 2016, 583-97 (Gold Access)

Brettschneider J, Thornby J, Nichols TE and Kendall WS
Spatial analysis of dead pixels
CRiSM Working Paper Series No. 14-24, 2014

Software

DetectorCheckerWebApp is an interactive WebApp for analysing pixel damage in CT scanners using the associated R-package DetectorChecker. Both have been developed jointly with The Alan Turing Institute and Prof Wilfrid Kendall. The project emerged as a spin off from our EPSRC *inside-out* blog. Initial versions of the software were issued on 29.3.2019 and new versions were released on 30.6.2020.

References

Modelling for microscopic images is joint work with Tom Honnor (Warwick Statistics, now UCL), Adam Johnson (Warwick Statistics), Steve Royle (Warwick Medical School)

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