TITLE

Planar point processes of blood capillary profiles:
Modelling and simulation on the basis of Strauss hard-core processes

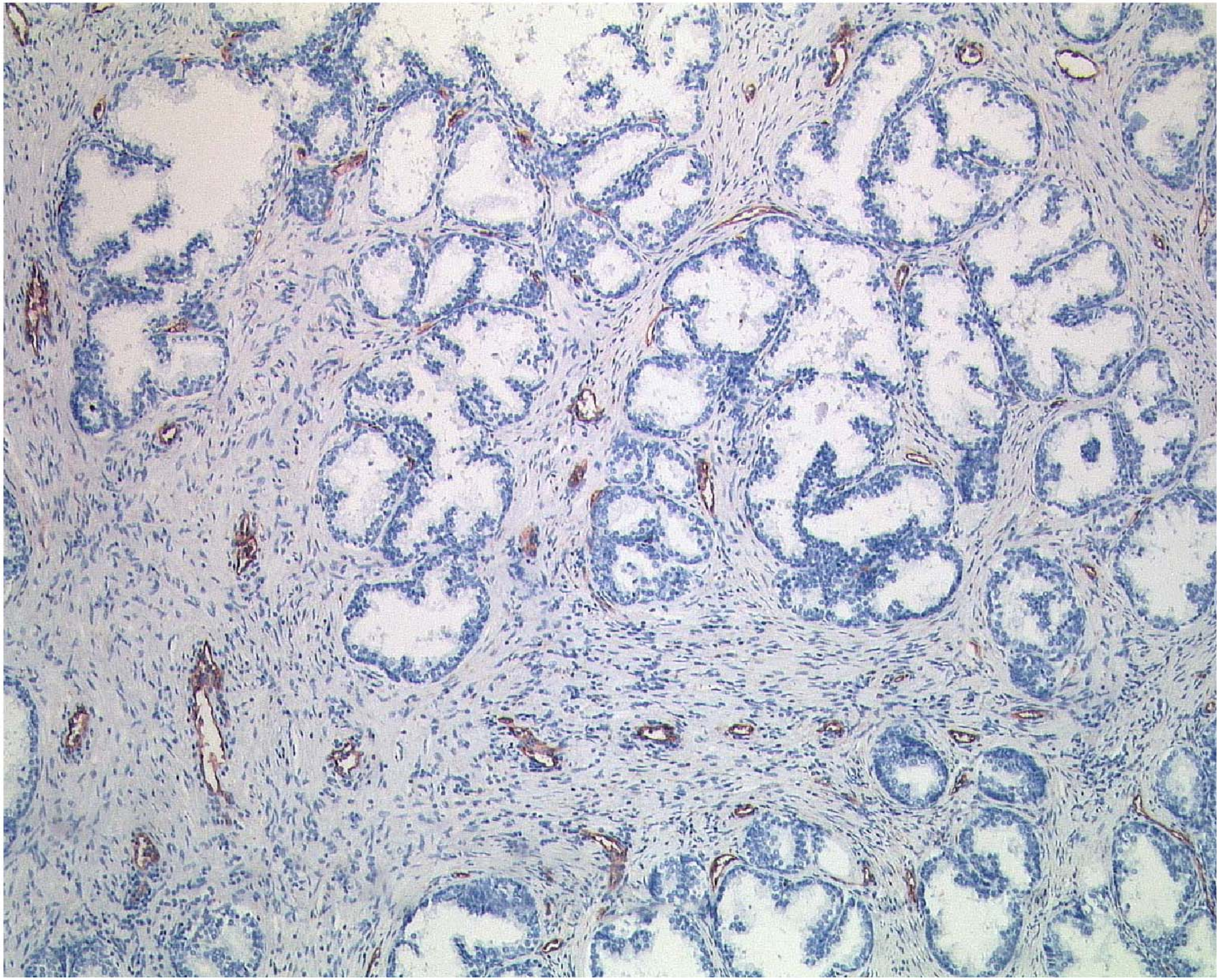
AUTHORS

Torsten Mattfeldt[1]
Stefanie Eckel[2]
Frank Fleischer[3]
Volker Schmidt[2]

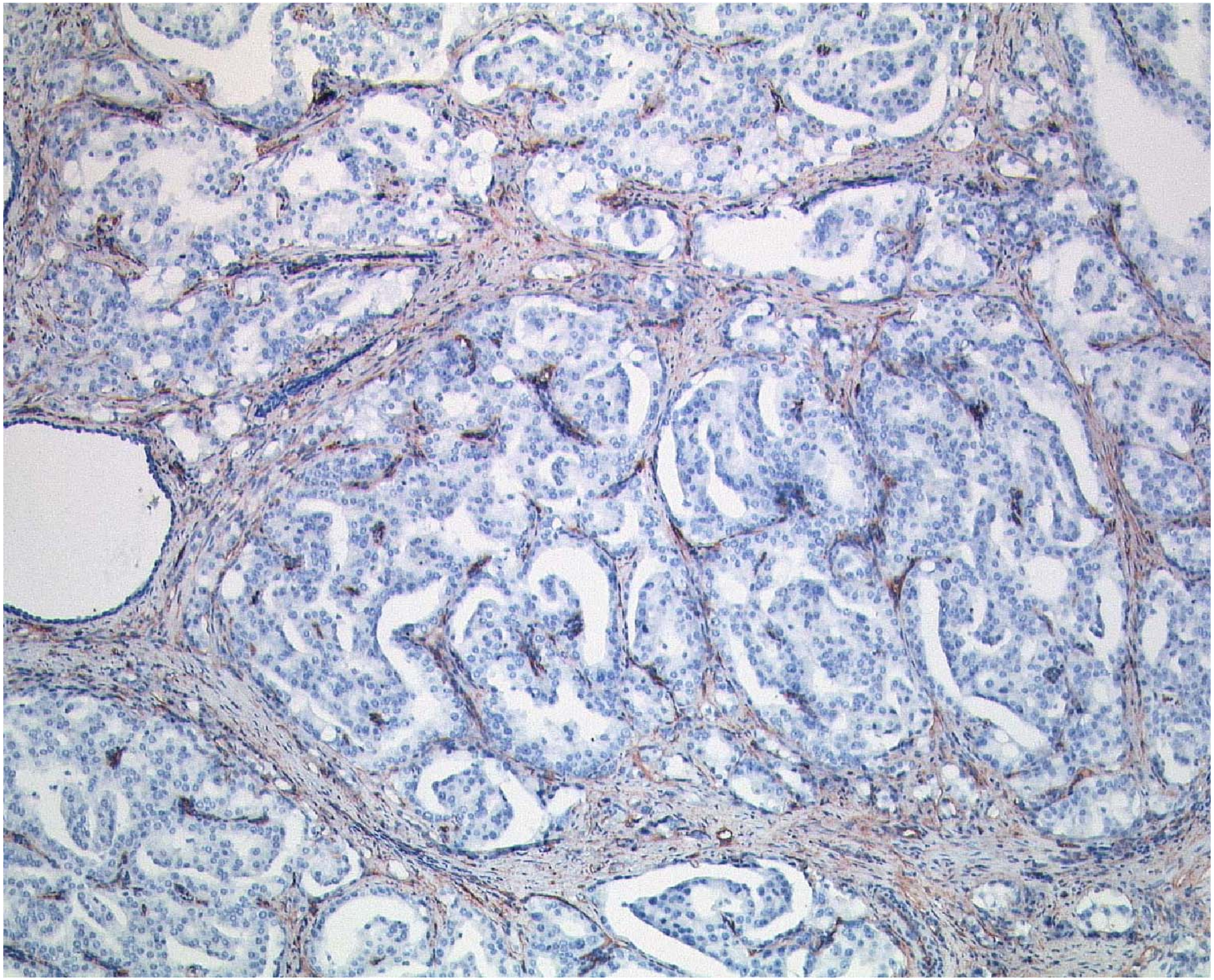
DEPARTMENTS

[1]Department of Pathology, University of Ulm
[2]Department of Stochastics, University of Ulm
[3]Department of Applied Information Processing & Department of Stochastics, University of Ulm

Söllerhaus-Workshop on Spatial Stochastic Modelling of Telecommunication Systems
28th March, 2006

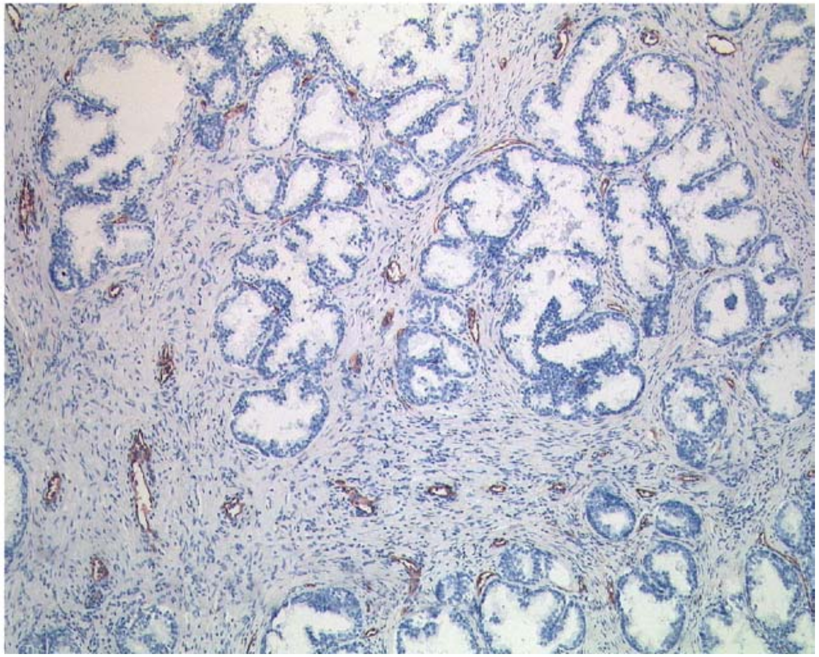


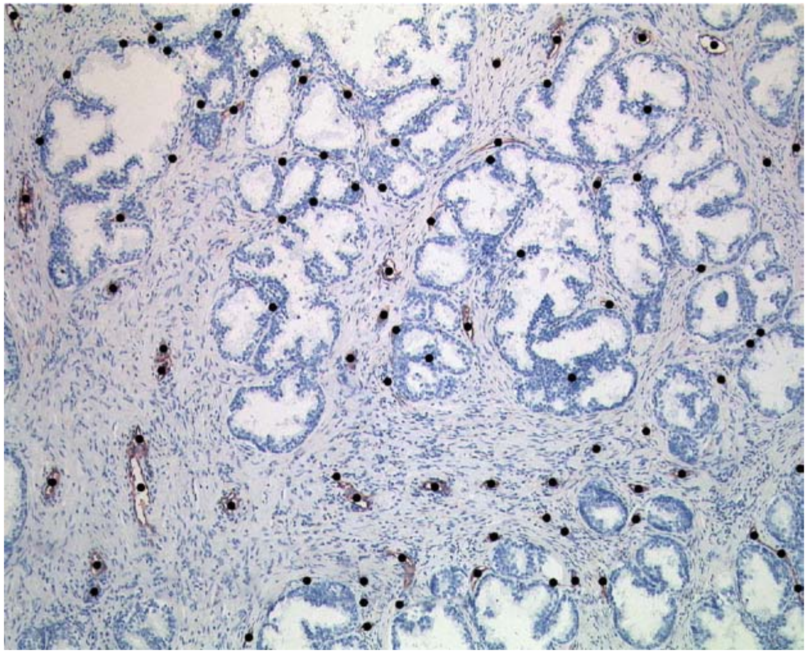
Tumour-free prostatic tissue, CD34 stain



Prostatic cancer, CD34 stain

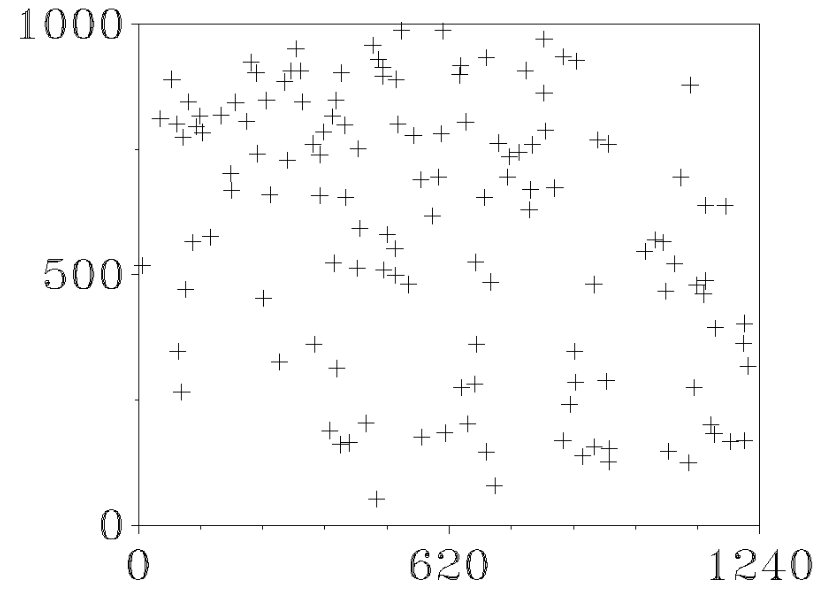
Detection of capillary profiles





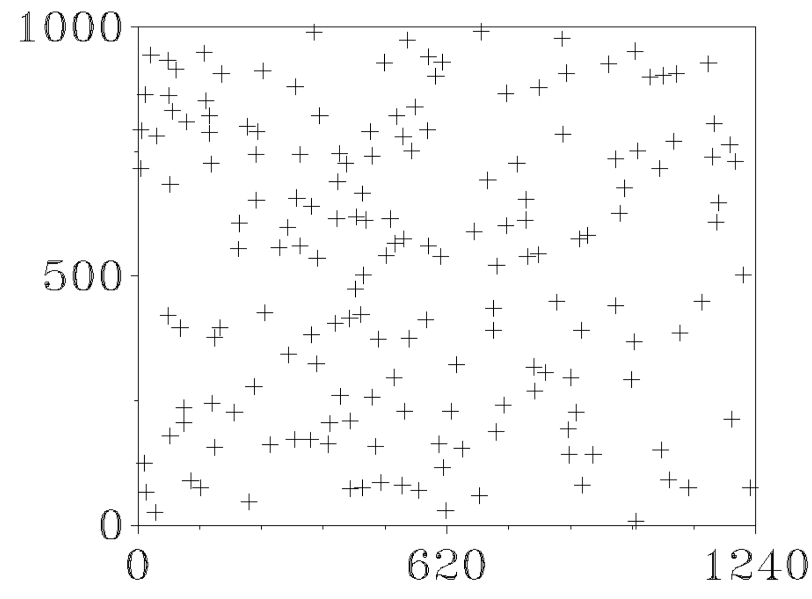
Normal case 1
Image 1

Original pattern



Carcinoma case 1
Image 1

Original pattern



EXPLORATIVE ANALYSIS OF PLANAR POINT PROCESSES

- Stationary planar point process X with intensity λ

- Second order K-function, reduced second moment function $K(r)$

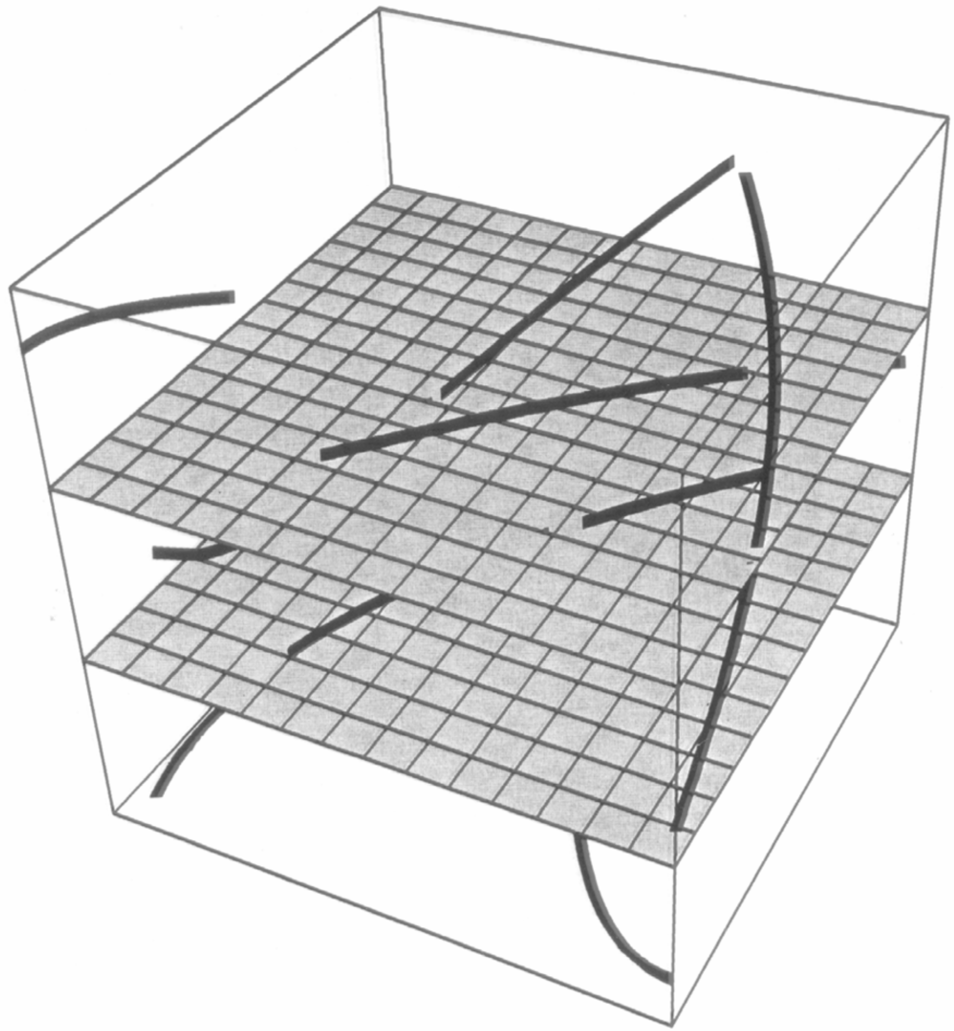
$$K(r) = \frac{E(\text{number of other points with distance} \leq r \;|(x,y) \in X)}{\lambda}$$

$$K_{Poi}(r) = \pi r^2$$

- Pair correlation function $g(r)$

$$g(r) = \frac{\varrho^{(2)}(r)}{\lambda^2} = \frac{1}{2\pi r} \frac{dK(r)}{dr}$$

$$g_{Poi}(r) = 1$$



Spatial fibre process

Isotropy

$L_V = 2\ Q_A$

REDUCED SECOND-ORDER FUNCTIONS OF SPATIAL FIBRE PROCESSES

- Stationary and isotropic spatial fibre process X with intensity L_V
- Reduced second order K-function $K_3(r)$

$$K_3(r) = \frac{E(\text{length of other fibres with distance} \leq r \ |(x,y,z) \in X)}{L_V}$$

$$K_{3\,Poi}(r) = (4\pi/3)r^3$$

- Reduced pair correlation function $g_3(r)$

$$g_3(r) = \frac{1}{4\pi r^2}\ \frac{dK_3(r)}{dr}$$

$$g_{3\,Poi}(r) = 1$$

- Stereological estimation

$$\widehat{g}_3(r) = \widehat{g}(r)$$

MATERIAL AND METHODS

Cases

Radical prostatectomy specimens
Normal: 12 cases, tumour-free domains
Cancer: 12 cases, domains with prostatic adenocarcinoma

Microscopy

Paraffin sections
Light microscopy
Immunohistochemistry for CD34

Image evaluation

Two rectangular fields per case
Size: 1240×1000 pixels (1860×1500 μm)
Interactive detection of centres of capillary profiles
Estimation of $g(r)$ for $r = 1$–500 pixels
Epanechnikov kernel
Bandwidth: $h = 0.1/\sqrt{\hat{\lambda}}$

ESTIMATION OF THE PAIR CORRELATION FUNCTION

- Estimation of the product density

$$\widehat{\varrho^{(2)}}(r) = \frac{1}{2\pi r} \sum_{X_i, X_j \in W_{\,i \neq j}} \frac{k_h(r - ||X_i - X_j||)}{|W_{X_i} \cap W_{X_j}|}$$

$$k_h(x) = \frac{3}{4h}(1 - \frac{x^2}{h^2}) 1_{(-h,h)}(x)$$

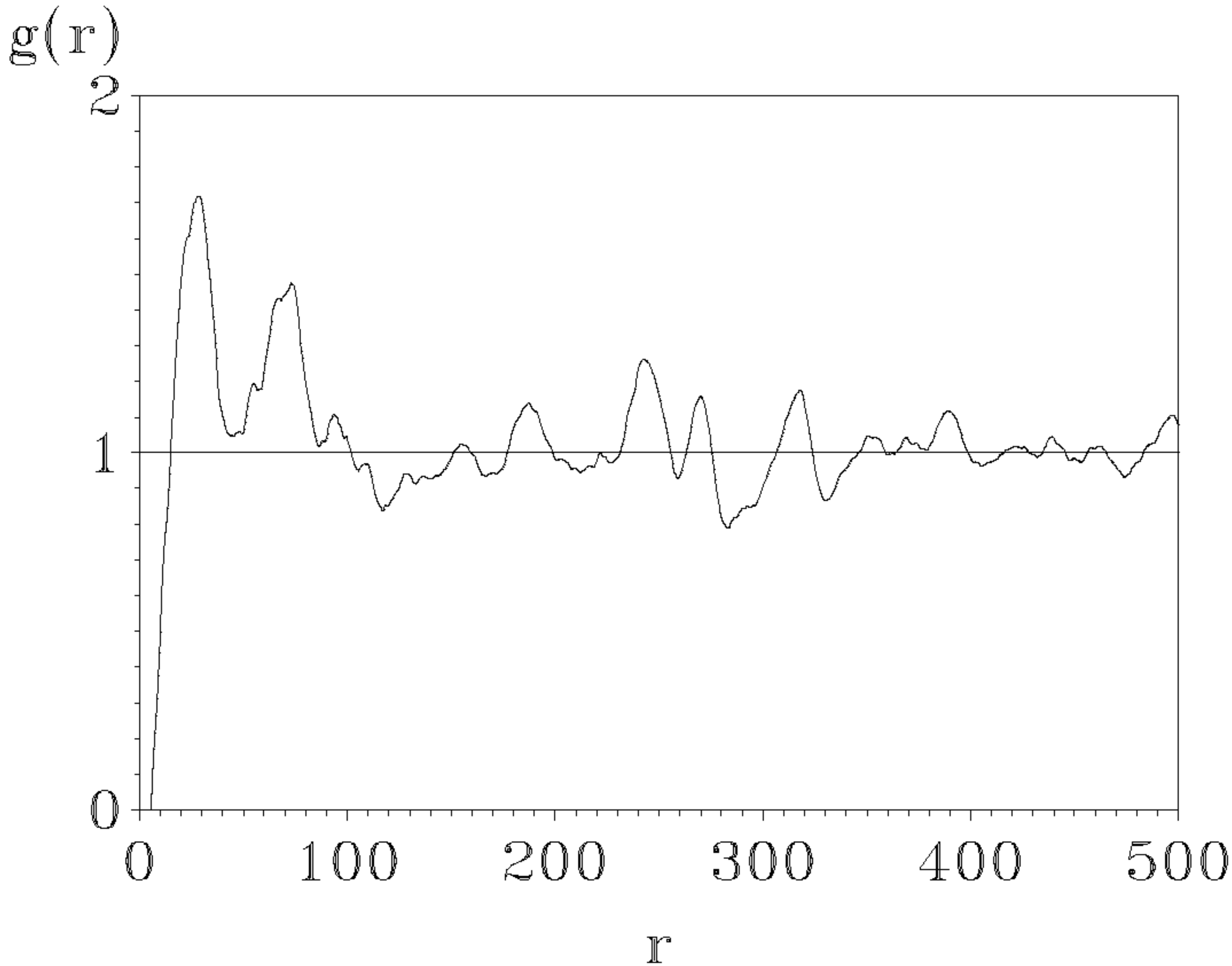
- Estimation of the squared intensity

$$\widehat{\lambda^2} = \frac{X(W)(X(W) - 1)}{|W|^2}$$

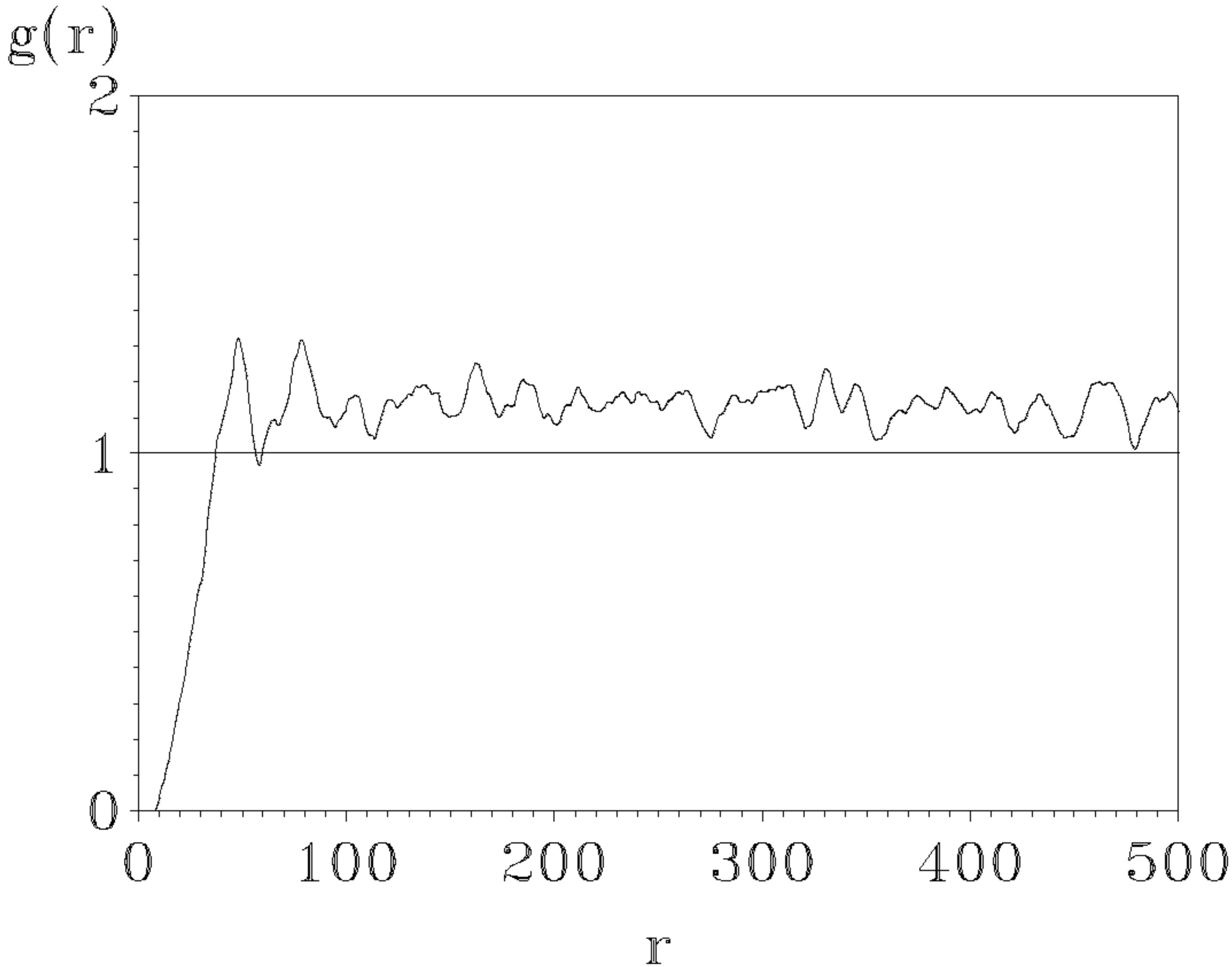
- Estimation of $g(r)$

$$\widehat{g}(r) = \frac{\widehat{\varrho^{(2)}}(r)}{\widehat{\lambda^2}}$$

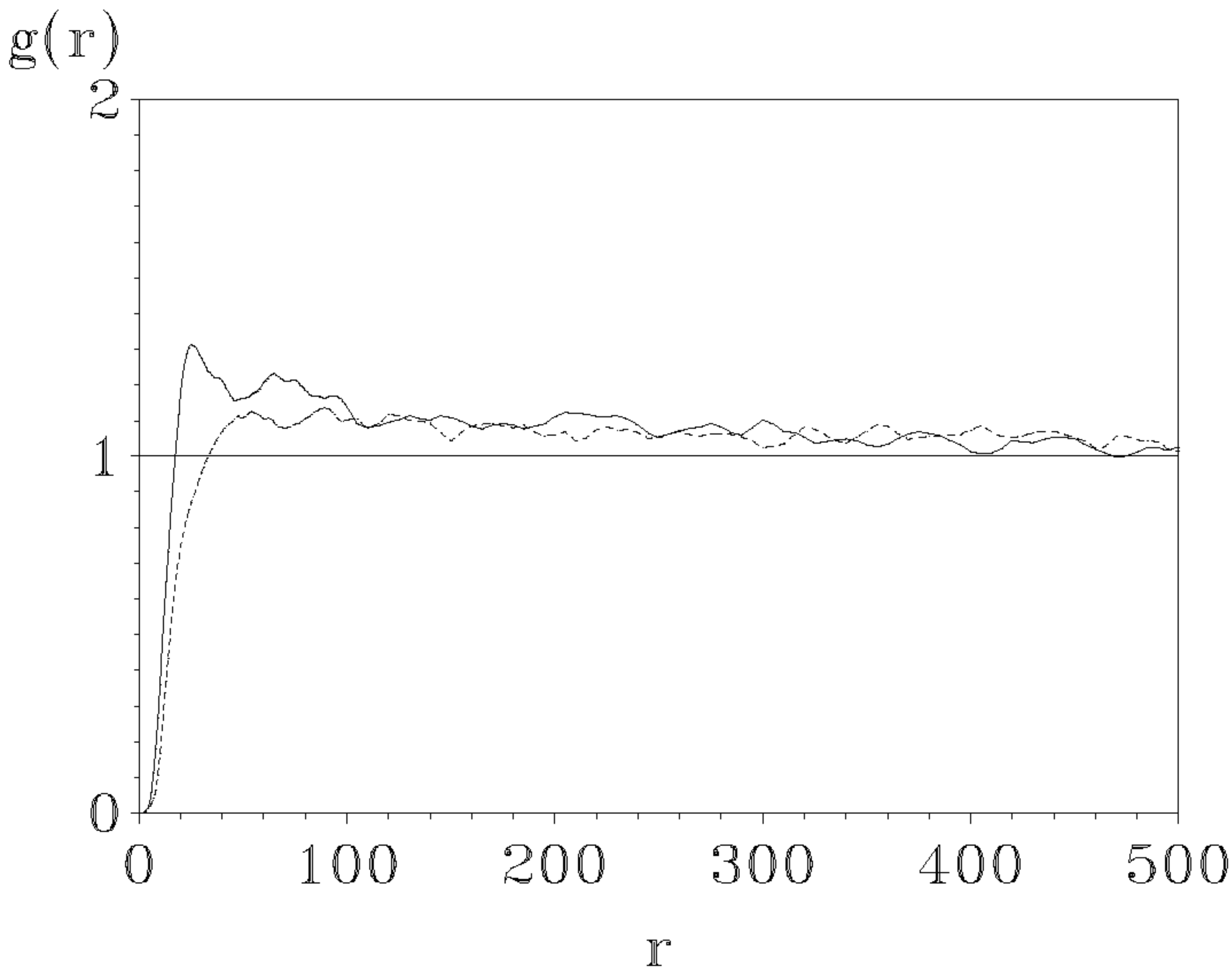
Reduced g-function: Normal case 9, field 1



Reduced g-function: Carcinoma case 3, field 2



Group comparison: —— Normal, ······ Carcinoma group



Local group comparisons of g-functions
Parametric methods

r	Normal $\bar{\widehat{g}}(r)$	Cancer $\bar{\widehat{g}}(r)$	D	t	$P(t)$	Significance level
5	0.0270	0.0192	0.0078	0.38	0.7096	
10	0.3599	0.1656	0.1944	2.69	0.0133	*
15	0.8100	0.5019	0.3081	3.31	0.0032	**
20	1.1770	0.7493	0.4278	4.13	0.0004	***
25	1.3117	0.8715	0.4402	4.73	0.0001	***
30	1.2738	0.9551	0.3187	3.67	0.0013	**
35	1.2254	1.0206	0.2047	2.46	0.0223	*
40	1.2106	1.0704	0.1402	2.04	0.0532	
45	1.1617	1.0978	0.0640	1.05	0.3047	
50	1.1616	1.1092	0.0524	0.88	0.3906	
55	1.1764	1.1237	0.0527	0.96	0.3473	
60	1.2049	1.1058	0.0991	2.20	0.0384	*
65	1.2313	1.0943	0.1369	3.22	0.0039	**
70	1.2099	1.0793	0.1306	2.57	0.0174	*
75	1.2149	1.0897	0.1252	2.41	0.0250	*
80	1.1846	1.1055	0.0792	1.49	0.1504	
85	1.1689	1.1251	0.0437	0.77	0.4519	
90	1.1633	1.1354	0.0278	0.52	0.6078	
95	1.1682	1.1076	0.0606	1.06	0.3000	
100	1.1377	1.1027	0.0350	0.67	0.5092	
200	1.1093	1.0606	0.0487	1.43	0.1672	
300	1.1002	1.0251	0.0750	2.29	0.0321	
400	1.0117	1.0732	−0.0610	−1.69	0.1055	
500	1.0256	1.0123	0.0133	0.46	0.6493	

EXPLORATIVE ANALYSIS OF PROSTATE CAPILLARIES
DISCUSSION OF FINDINGS

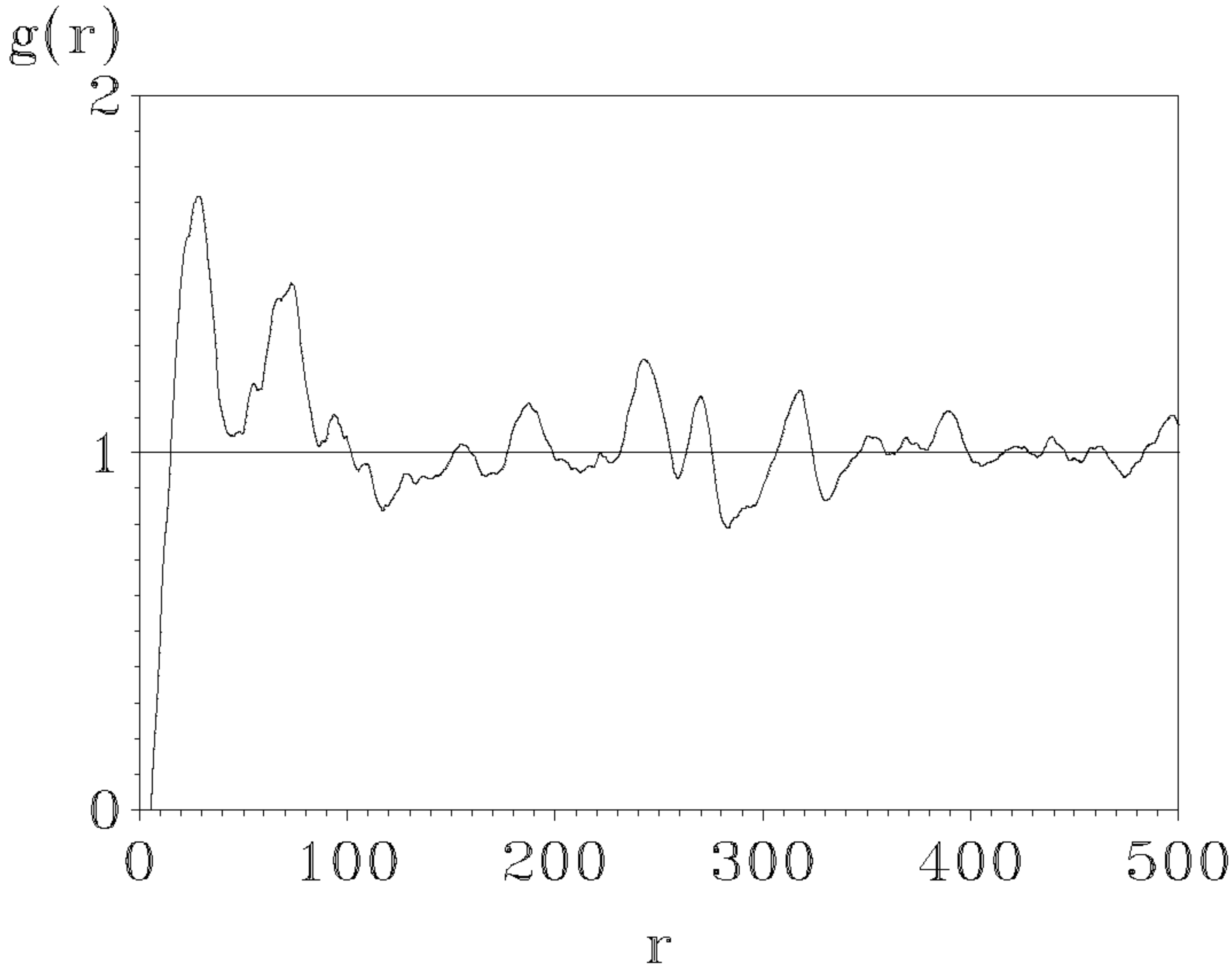
Malignant transformation

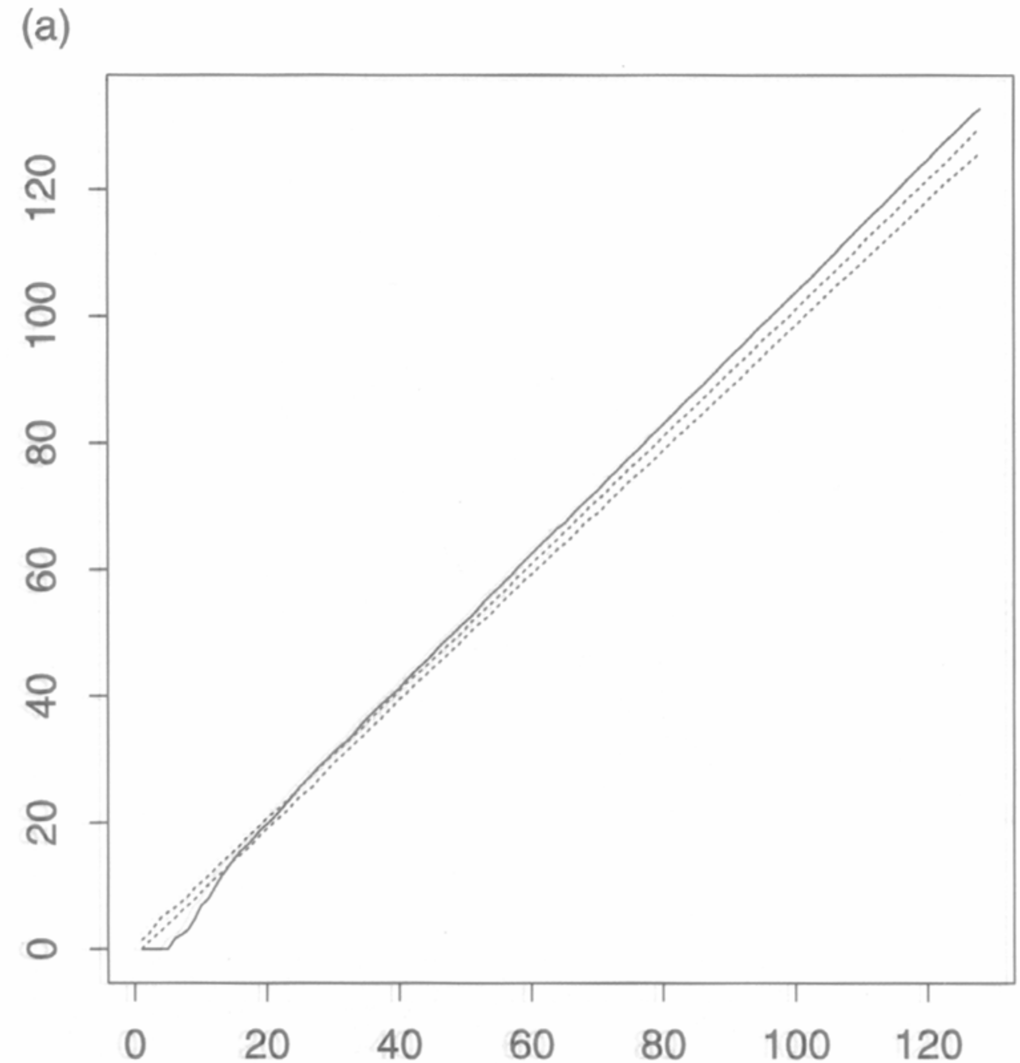
- Increase of intensity L_V
- Unchanged hard-core distance
- Changes of second-order properties
- Two domains with changed short-range interaction

Capillary geometry

- Parametric modelling
- Hard-core model
- Clustering at longer ranges

Reduced g-function: Normal case 9, field 1





Schladitz, K., Särkkä, A., Pavenstädt, I., Haferkamp, O., Mattfeldt, T. (2003)
Statistical analysis of intramembranous particles using freeze fracture specimens.
J. Microsc. 211, 137-153.

POINT PROCESS MODELLING

Model

Nonstationary Strauss hard core process

Trend

Harmonic polynomial

$$\lambda(x, y) = \exp\left(a_0 + a_1 x + a_2 y + a_3 xy + a_4(x^2 - y^2)\right)$$

Fitting of coefficients a_1–a_4 and intercept a_0

Visualization: Perspective plot

Interaction

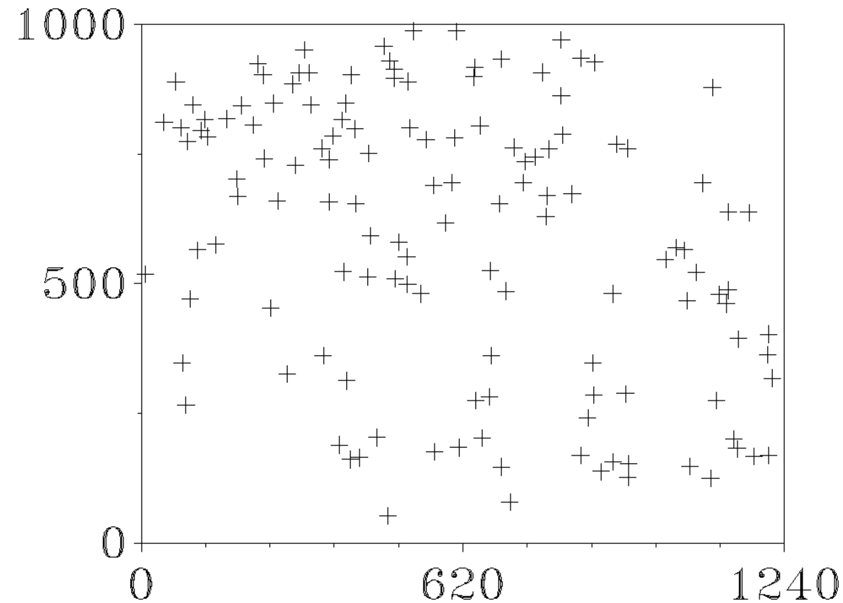
Strauss hard core process

Fitting of three parameters

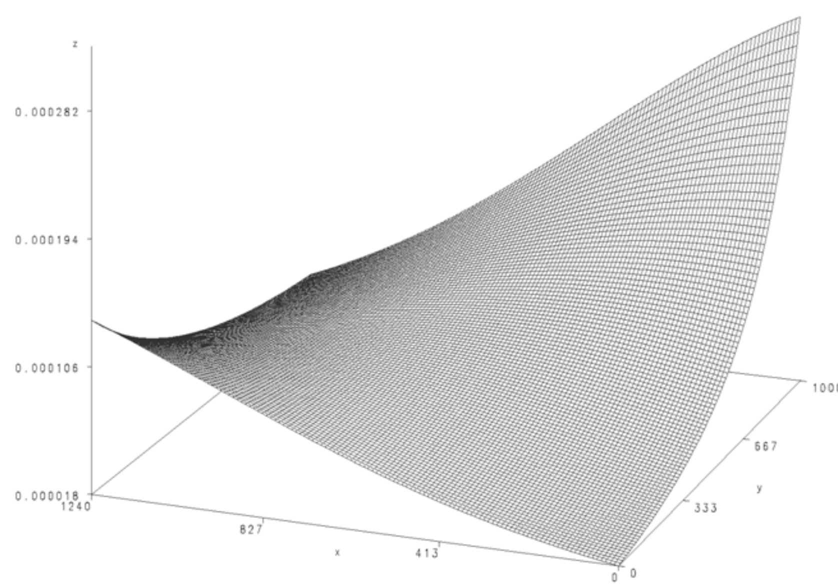
Software

Package *spatstat* under R 2.2.0 under Linux (Baddeley & Turner, 2005)

Normal case 1, image 1
Original pattern



Normal case 1, image 1
Perspective plot of the trend



FITTING OF THE STRAUSS HARD CORE MODEL

PROBABILITY DENSITY

$$
\begin{array}{ll}
f(r) = 0 & \text{if } 0 \leq r \leq r_0 \\
f(r) = \alpha\beta\gamma^{s(r)} & \text{if } r_0 < r \leq R \\
 & \quad \text{if } (\gamma > 1)\text{: Clustering} \\
 & \quad \text{if } (\gamma < 1)\text{: Inhibition} \\
 & \quad \text{if } (\gamma = 1)\text{: Classical hard core process} \\
f(r) = 1 & \text{if } r > R
\end{array}
$$

IRREGULAR PARAMETERS

Hard core distance r_0

Estimator: minimum interpoint distance

Interaction radius R

Method: profile maximum pseudolikelihood
Edge correction: Translation
Quadrature scheme = data + dummy + weights
Dummy quadrature points: 30×30 grid, plus 4 corner points

REGULAR PARAMETER

Interaction parameter γ

Group comparisons of model parameters

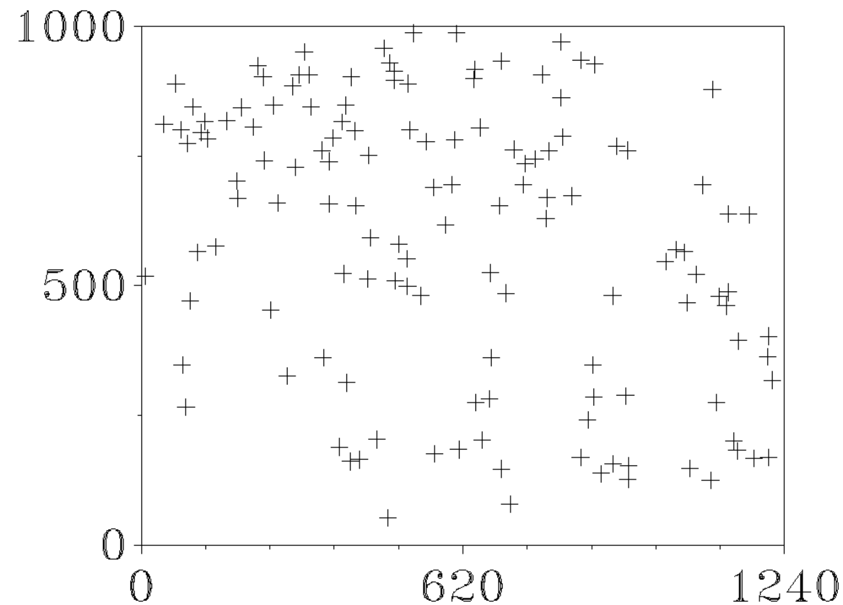
	Normal group $\bar{x}$	SD	Cancer group $\bar{x}$	SD	t	Level of significance
Intensity						
N(cap/field)	127	38	188	60	2.98	$p < 0.01$
λ(points/pixel^2)	0.000102	0.000031	0.000152	0.000048	2.98	$p < 0.01$
Strauss hard core model						
r_0 (pixel)	17.33	4.51	15.33	4.02	1.62	N. S.
R (pixel)	51.37	29.31	51.29	22.48	0.01	N. S.
γ	1.912	1.049	0.886	0.416	4.45	$p < 0.0001$

SIMULATION OF PLANAR POINT PROCESSES USING THE METROPOLIS-HASTINGS ALGORITHM

Concept	**Contents**
Model	Strauss hard core process
Target density	Probability density of the model
Principle	Markov chain Monte Carlo method
Markov chain	Point processes
Number of points	fixed (conditional simulation)
Start pattern	Poisson point process with the same number of points
Proposal	move of a single point ($p = 1$; no birth, no death)
Update	acceptance of the proposal
	or status quo
	according to random number
Iterations	$n_{rep} = 100000$ (Ripley's rule of thumb: $10 \times N \approx 3500$)
Aim	Convergence to point processes with the target density

Normal case 1
Image 1

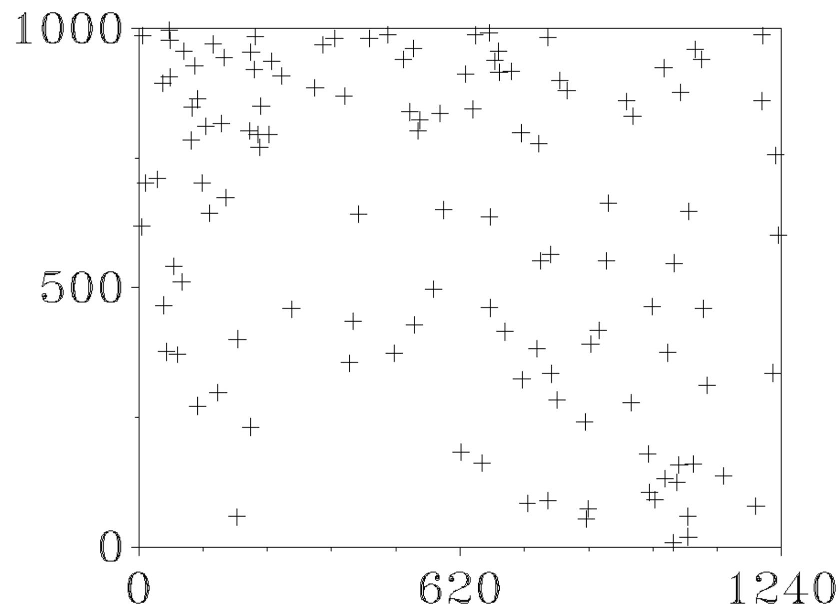
Original pattern



Normal case 1
Image 1
Simulation #1 of 999

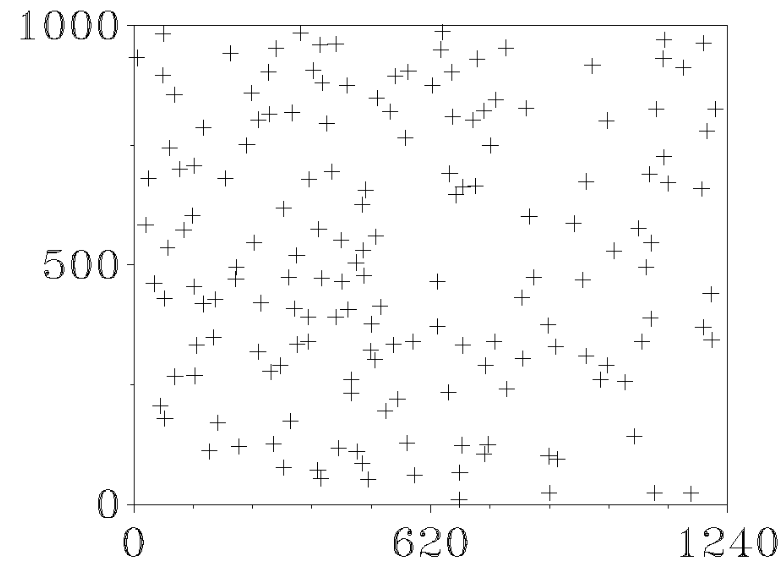
Strauss hard core process
with the same intensity

N=134, r_0=16, R=35, γ=1.667



Carcinoma case 1
Image 1

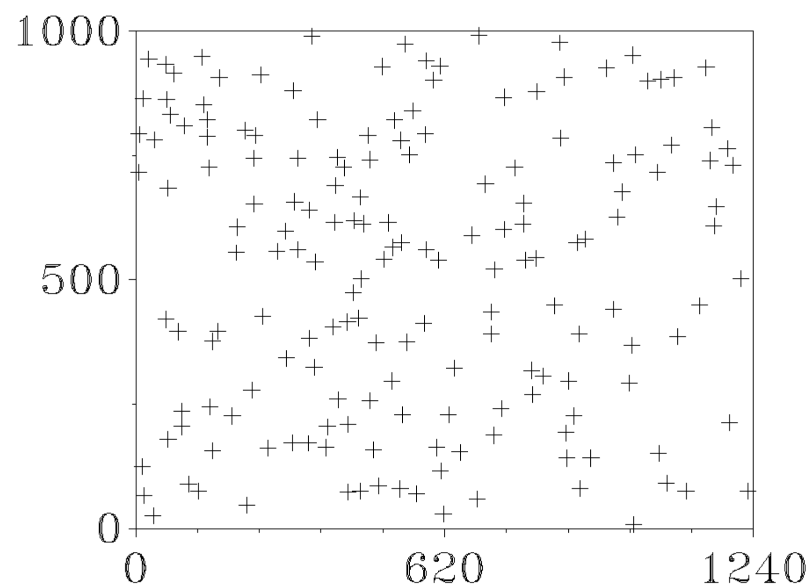
Original pattern



Carcinoma case 1
Image 1
Simulation #1 of 999

Strauss hard core process
with the same intensity

N=173, r_0=17, R=30, γ=0.636



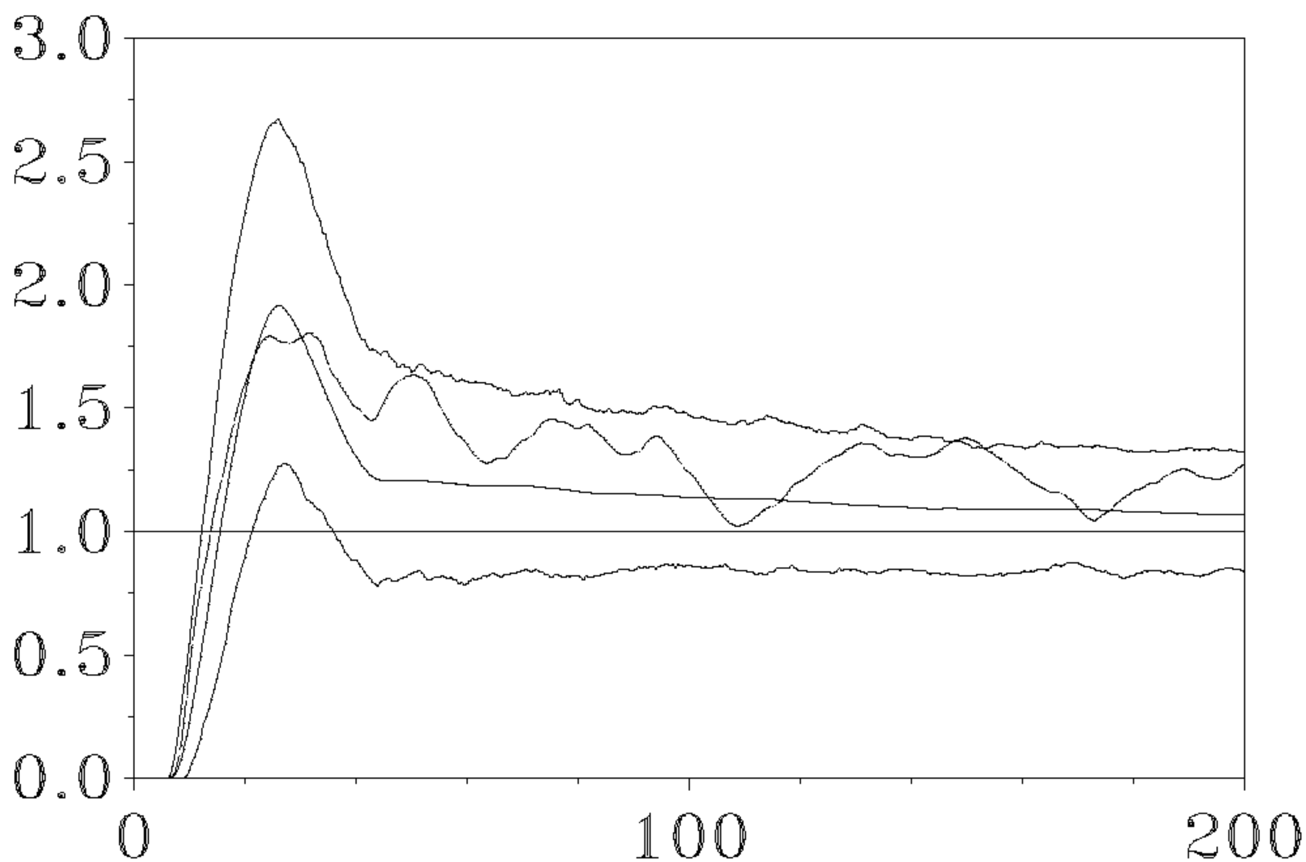
Normal case 1, Image 1: Pair correlation function g(r)

- True sample
- Simulations 1–999

Strauss hard core process

N=134, r_0=16, R=35, γ=1.667

Plots of mean values, g_{26} and g_{975}



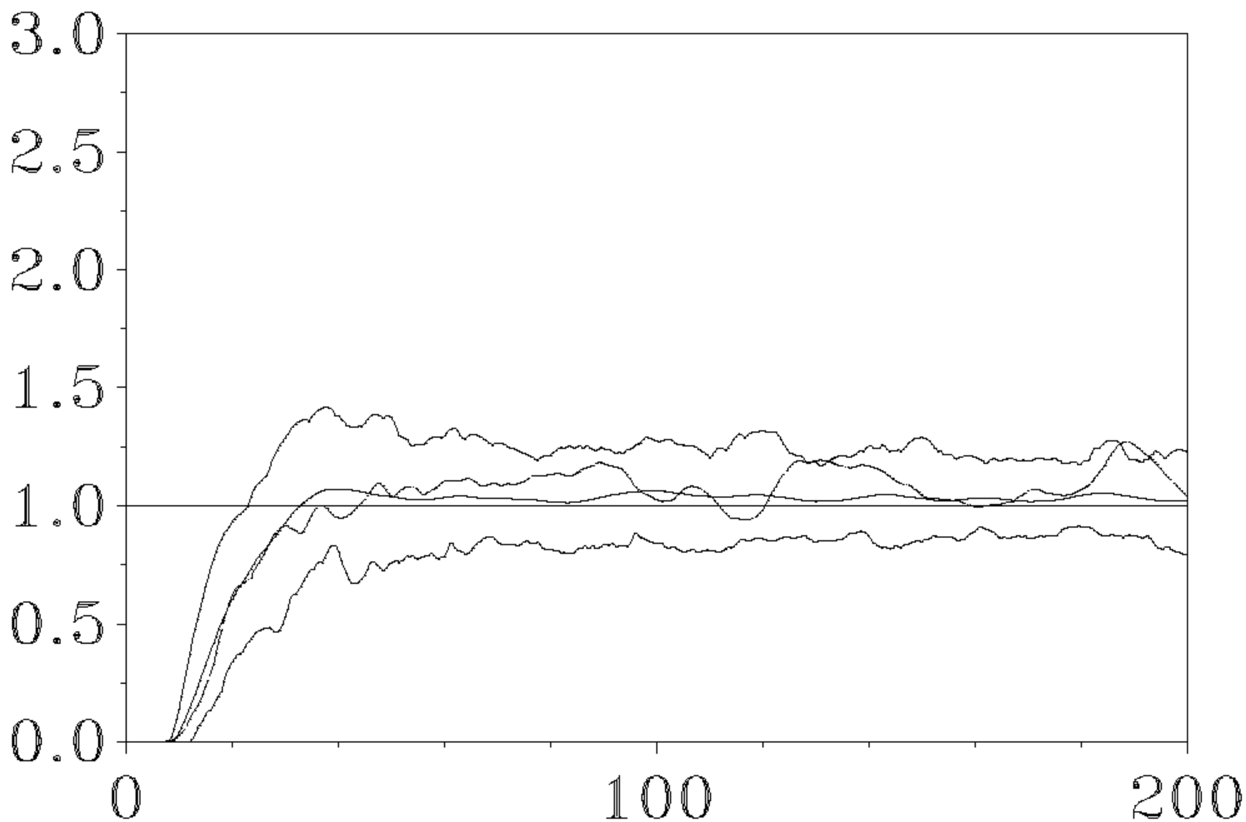
Carcinoma case 1, Image 1: Pair correlation function g(r)

- True sample
- Simulations 1–999

Strauss hard core process

N=173, r_0=17, R=30, γ=0.636

Plots of mean values, g_{26} and g_{975}



EFFECT OF NONSTATIONARITY (TREND) ON THE GOODNESS OF FIT

COMPUTATIONS

- Residuals between real data and model expectation as measure of the goodness of fit
- Local (r-wise) differences between $g(r)$ of the sample and the mean $g(r)$ of the 999 simulations
- Sum of squared differences for all r
- Model fitting: Strauss hard core process with and without trend component

RESULTS

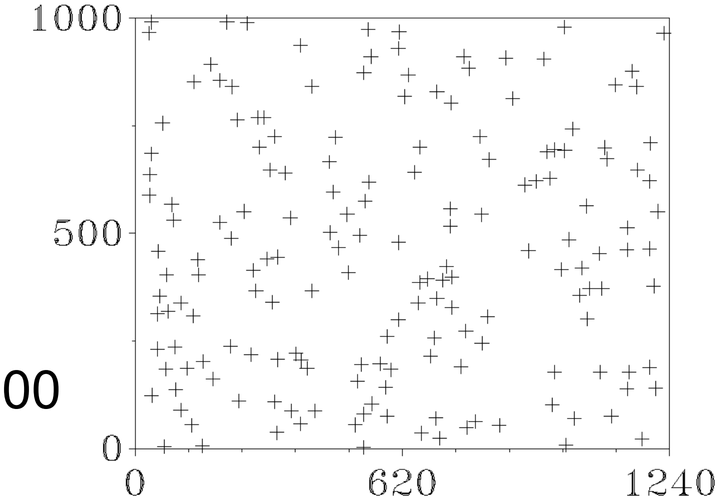
	Normal		Tumour	
	Image 1	Image 2	Image 1	Image 2
Stationary	23.4	25.0	9.79	17.1
Nonstationary	21.1	24.7	9.67	16.5

CONCLUSION

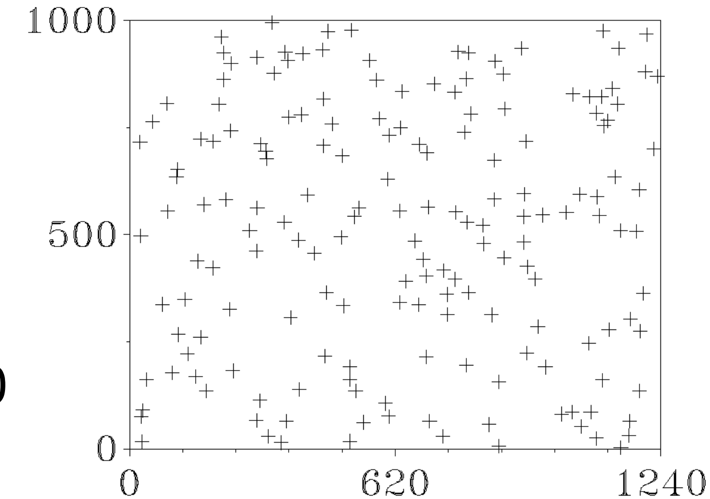
- Consideration of trend does not improve the goodness of fit significantly in our application

Strauss hard core process: Simulations with N=173, r_0=17, R=30, γ=0.636

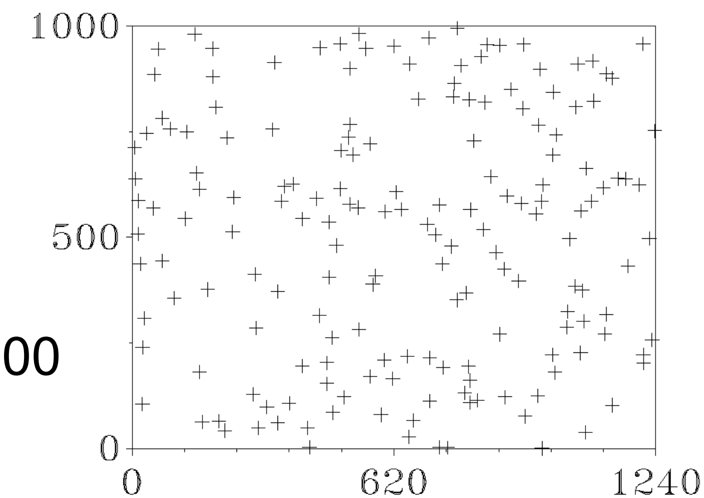
t=1000



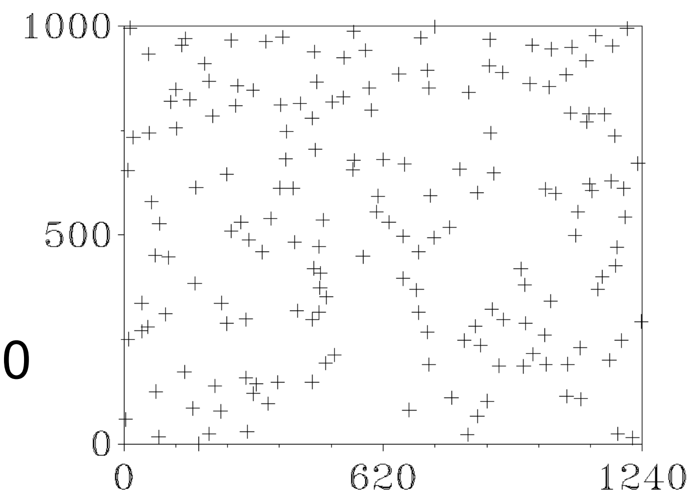
t=10000



t=5000



t=100000



Pair correlation functions

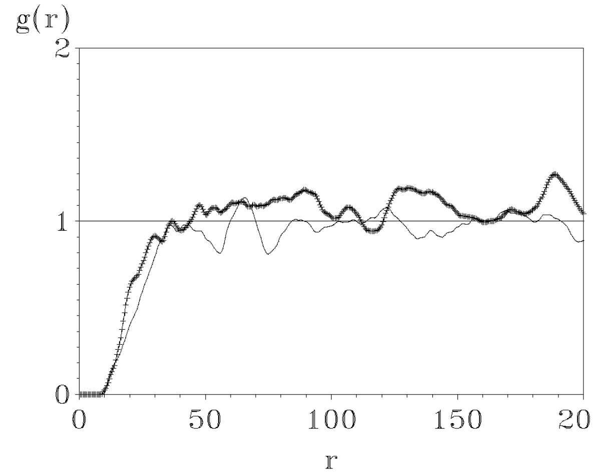
True sample ++++++++

Carcinoma Case 1, image 1

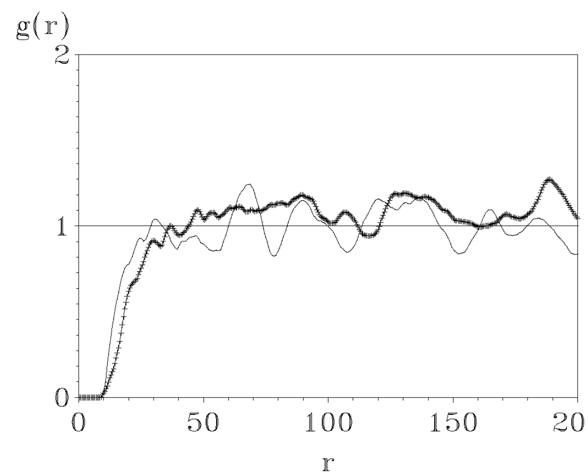
Strauss hard core process

Simulations with N=173, r_0=17, R=30, γ=0.636 ....

T=50000

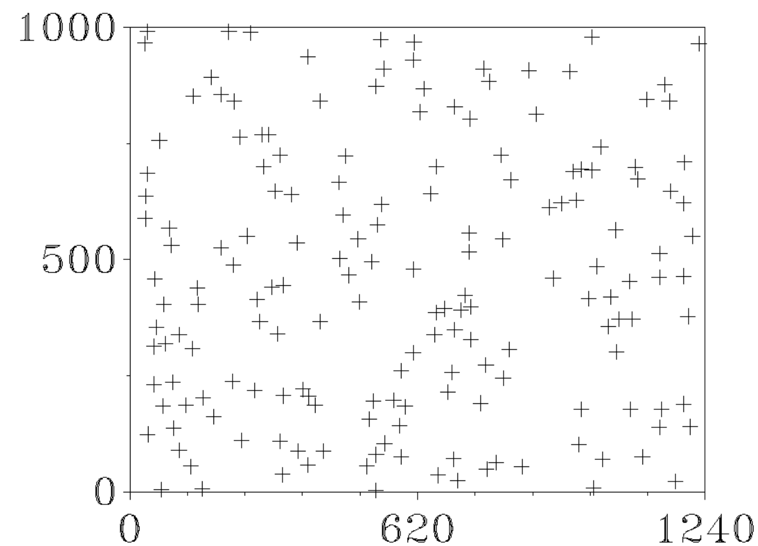


T=100000

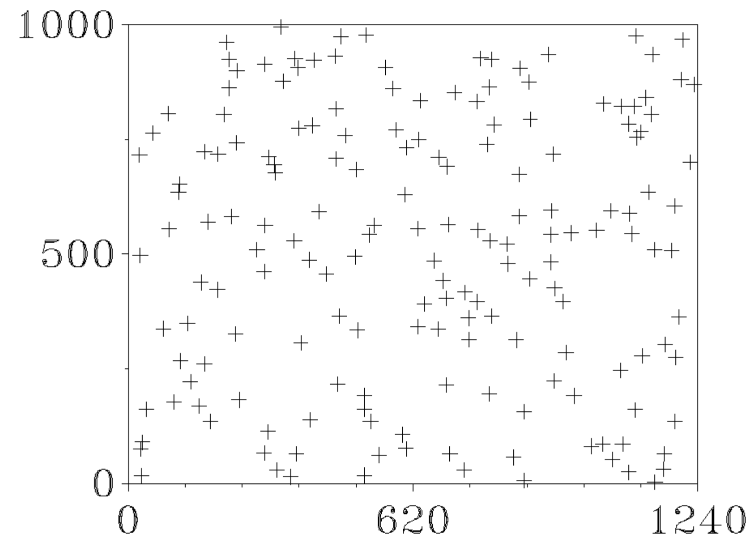


Strauss hard core process
Simulations with N=173, r_0=17, R=30, γ=0.636, t=100000

Start process:
Original pattern
Carcinoma Case 1, image 1



Start process:
Poisson process
with the same intensity



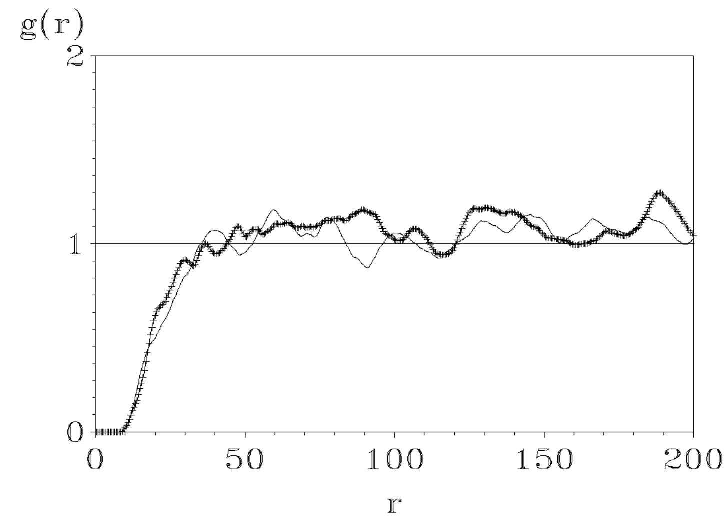
Pair correlation functions

True sample ++++++++

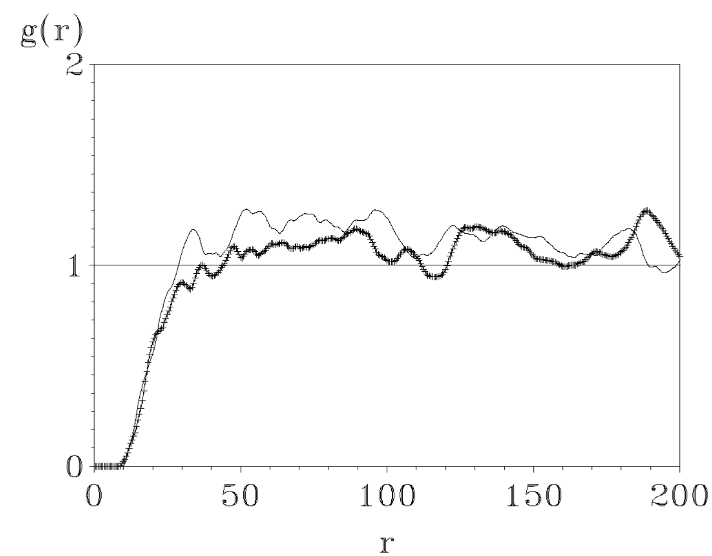
Strauss hard core process:

Simulations with N=173, r_0=17, R=30, γ=0.636, t=100000 ....

Start process:
Original pattern
Carcinoma Case 1, image 1



Start process:
Poisson process
with the same intensity



POINT PROCESSES OF CAPILLARY FIBRE PROFILES OF GLANDULAR TISSUES: CONCLUSIONS

General

Modelling and simulation feasible with *spatstat* software
Consideration of trend does not improve the goodness of fit
Compatible with stationary Strauss hard core process

Findings in tumour tissue

Normal tissue: interaction parameter $\gamma > 1$
Tumour tissue: interaction parameter $\gamma < 1$
Decreased clustering behaviour for distances between r_0 and R in the tumour tissue
Changes of model parameters consistent with results of explorative statistics

Outlook

Improved graphical analysis of spatial residuals (A. Baddeley)
- Residuals with respect to trend surface
- Interaction: Q–Q plots

Improved monitoring of convergence
Export of methods to other data sets (thesis Paul Grahovac: prostate carcinoma cell nuclei)