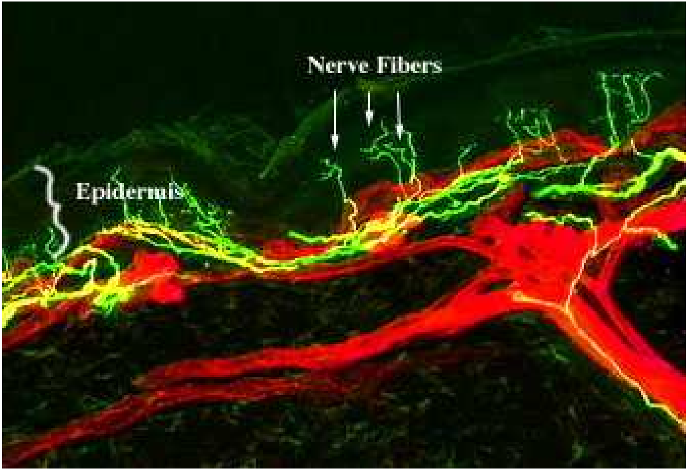
Modelling Epidermal Nerve Fibre Patterns

Smögen Workshop 2006

Background

ENFs

- Sensory fibres in the epidermis, (heat, pain etc)
- Existence not conclusively established until 1990:s (Wang *et al.* (-90) and Kennedy *et al.* (-93))
- Cover the body
- What happens as diabetes progress?
  - Fewer fibres
  - Clustering
  - Total fiber length decreases
  - Individual branches may lengthen (to compensate for nerve loss)


Nerve Fibers
Epidermis

Diabetic Neuropathy (Peripheral)

- toes,feet,legs,hands,arms
- Symptoms
  - numbness or insensitivity to pain or temperature
  - a tingling or burning sensation
  - sharp pains or cramps
  - extreme sensitivity to touch
  - loss of balance and coordination

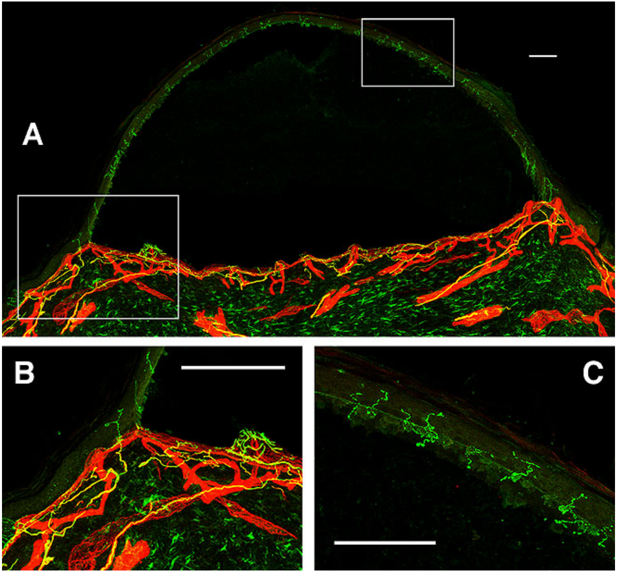
- Early diagnose when disease is more likely to respond to treatment

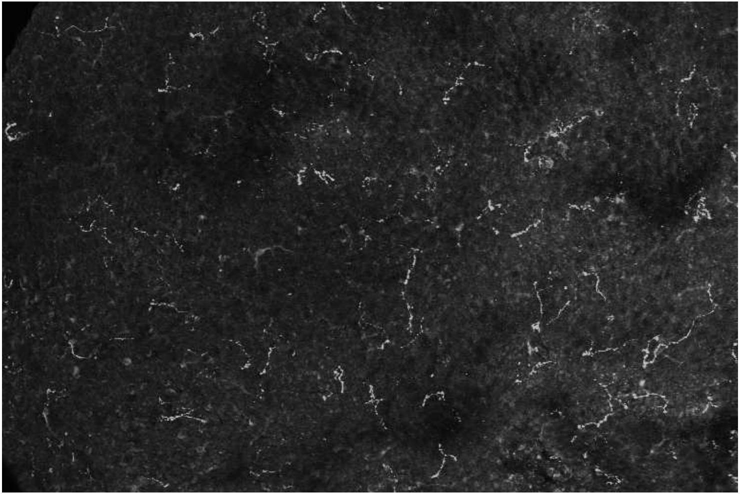
- Changes in ENF patterns before symptoms

Data

- Suction-induced skin biopsy
- Digitized images (510×765 pixels)
- Pixel size $\approx 0.83 \times 0.83$ microns

- Non-diseased (*Normal*) and 3 disease-states (*Mild*, *Moderate* and *Severe*)
- Only 7 samples (1 Normal and 2 from respective disease state)


A
B
C



- Analysis
  - Regard pattern of trunks as a realization of a planar point process
  - Regard fibre pattern as a realization of a planar fibre process
  - Compare between diseased and normal patterns
- Modelling

Modelling

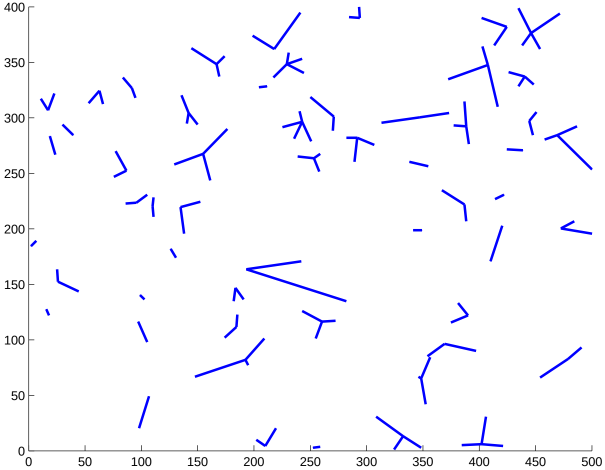
Characteristics

- Interaction
- Coverage

Simplifications

- Replace branches by line segments
  - Only nerve endings transmit sensations

- ENFs in $\mathbb{R}^3$
- Modelled in $\mathbb{R}^2$
  - Most spatial variation is in two dimensions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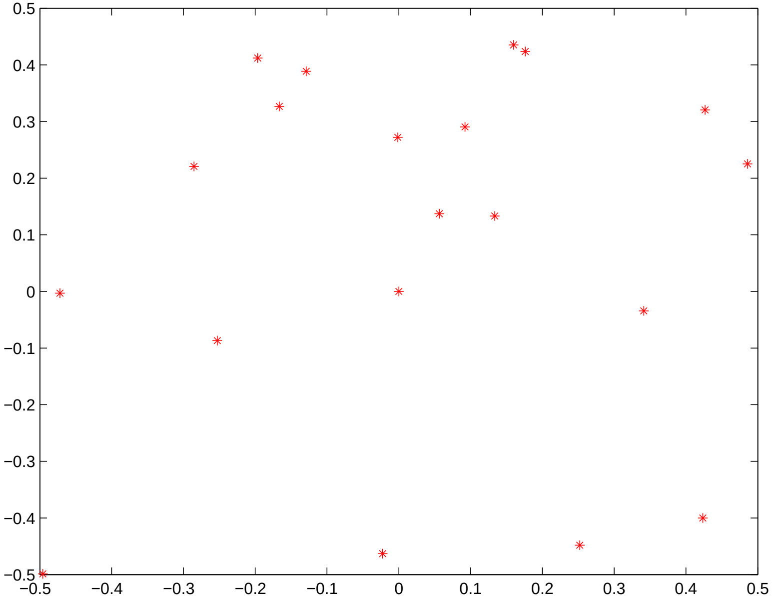
Definition

Model

- Two independent, homogenous Poisson processes in $\mathbb{R}^2$, Φ_e and Φ_b having intensities λ_e and λ_b, respectively.
- Each point in Φ_e is connected by a line segment to the closest point in Φ_b

Foss, S, Zuyev, S (1996) *On a Voronoi Aggregative Process Related to a Bivariate Poisson Process*, Adv. Appl. Prob., 28, pp. 965-981.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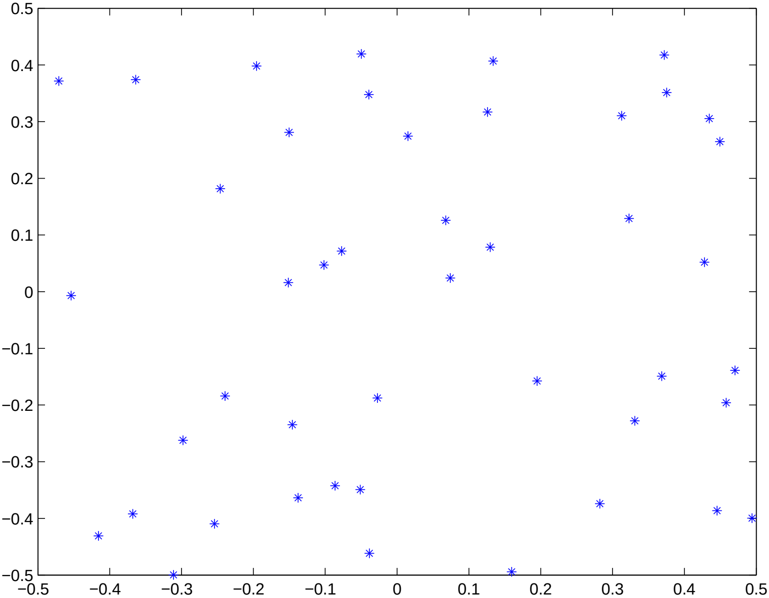
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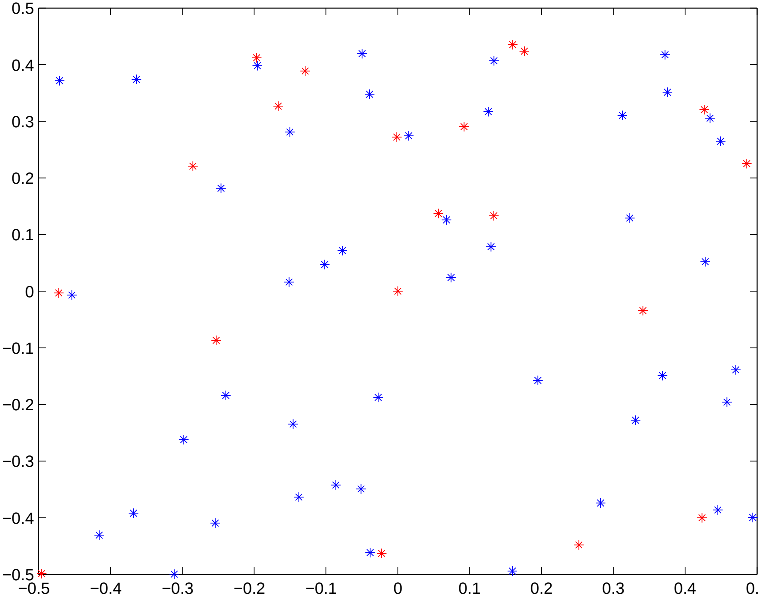
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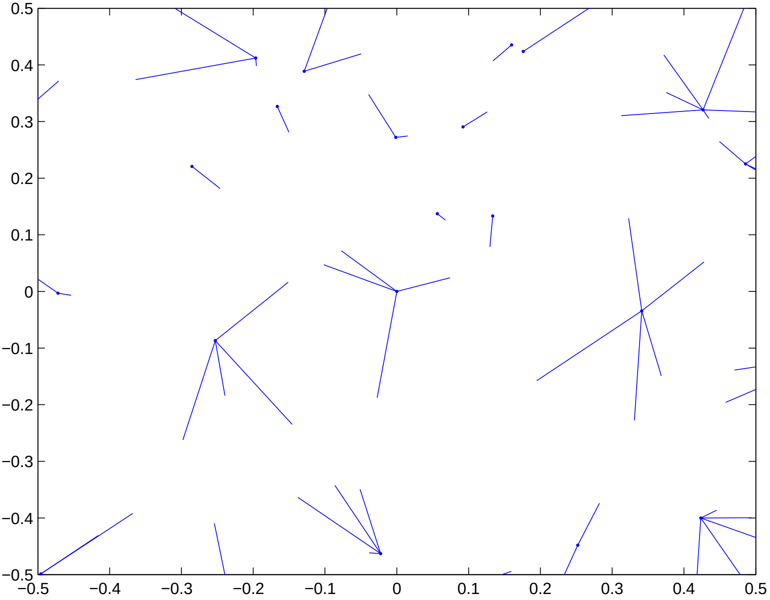
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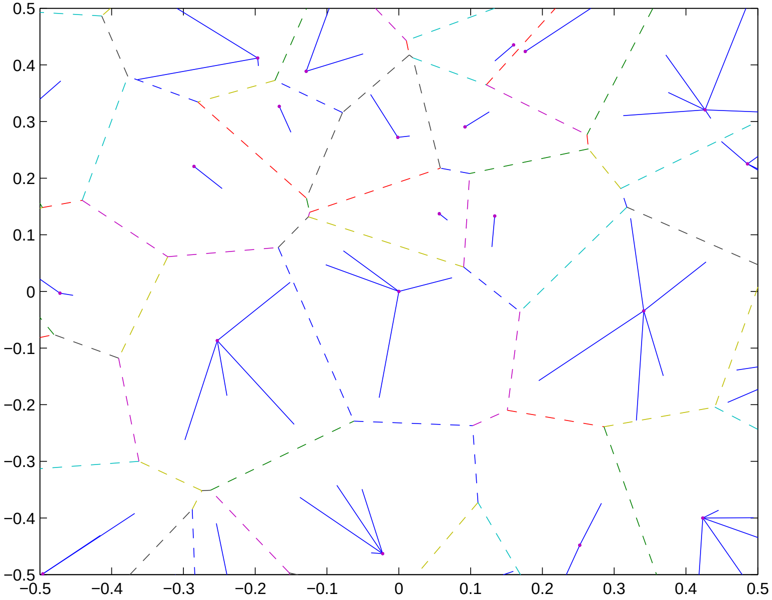
Definition

- Let $\mathcal{V}_{\Phi_b}$ denote the Voronoi tessellation generated by the base process
- $\mathcal{V}_{\Phi_b} = \bigcup_{\mathbf{y}\in\Phi_b} \mathcal{V}_{\Phi_b}(\mathbf{y})$, where

$$\mathcal{V}_{\Phi_b}(\mathbf{y}) = \{\mathbf{x} \in \mathbb{R}^2;\ |\mathbf{x}-\mathbf{y}| \leq |\mathbf{x}-\mathbf{z}|\,\forall\,\mathbf{z} \in \Phi_b \backslash \{\mathbf{y}\}\}$$

- All endings connected to $\mathbf{x} \in \Phi_b$ is the set $\Phi_e \cap \mathcal{V}_{\Phi_b}(\mathbf{x})$
- The *typical* cell: $\mathcal{V}_o$, the origin is the nucleus of this cell.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We can regard Φ_b as a marked point process, i.e.

$$\Phi_b = \{[x_n; m_n]\},$$

where x_n is the location and m_n the mark at this location.

The marks can be e.g.

- Number of branches: N
- Total Branch Lengths: L

- mark distributions?

$$N_o \sim \mathrm{Poi}(\lambda_e |\mathcal{V}_o|)$$

$$|\mathcal{V}_o| \sim ?$$

Calka, P (2003) *Precise formulae for the distributions of the principal geometric characteristics of the typical cells of a two-dimensional Poisson-Voronoi tessellation and a Poisson line process*, Adv. in Appl. Probab., 35 , pp. 551-562.

$$L_o \stackrel{\mathcal{L}}{=} \sum_{i=1}^{N_o} B_i$$

$$F_B(r) = P(B < r) = \frac{1}{\lambda_e |A|} \mathbb{E}\left[\sum_{\mathbf{x} \in \Phi_e \cap A} \mathbf{1}_{\{\Phi_b(b(\mathbf{x},r))>0\}} \right],$$

for an arbitrary set $A \subset \mathbb{R}^2$ s.t. $0 < |A| < \infty$.

$$F_B(r) = H_b(r) = 1 - \mathrm{e}^{-\lambda_b \pi r^2}.$$

For any measurable function $g : \mathbb{R}^2 \to \mathbb{R}_+$, define

$$\Sigma_g = \sum_{\mathbf{x} \in \Phi_e} g(\mathbf{x}) \mathbf{1}_{\{\mathbf{x} \in \mathcal{V}_o\}}.$$

N_o and L_o are special cases of Σ_g, with $g(\mathbf{x}) = 1$ and $g(\mathbf{x}) = |\mathbf{x}|$, respectively, i.e.

$$N_o = \sum_{\mathbf{x} \in \Phi_e} \mathbf{1}_{\{\mathbf{x} \in \mathcal{V}_o\}}$$

$$L_o = \sum_{\mathbf{x} \in \Phi_e} |\mathbf{x}| \mathbf{1}_{\{\mathbf{x} \in \mathcal{V}_o\}}$$

- $\mathbb{E}[\Sigma_g]$?
- $\mathrm{Cov}(\Sigma_{g_1}, \Sigma_{g_2})$?

Theorem 1

$$\mathbb{E}[\Sigma_g] = \lambda_e \int_{\mathbb{R}^2} g(\mathbf{x}) \mathrm{e}^{-\lambda_b \pi |\mathbf{x}|^2} d\mathbf{x}$$

Theorem 2 For $g_1, g_2 : \mathbb{R}^2 \to \mathbb{R}_+$ measurable

$$\begin{aligned} &\mathrm{Cov}\left(\Sigma_{g_1}, \Sigma_{g_2}\right) \\ &= \lambda_e \int_{\mathbb{R}^2} g_1(\mathbf{x}) g_2(\mathbf{x}) \mathrm{e}^{-\lambda_b \pi |\mathbf{x}|^2} d\mathbf{x} \\ &\quad + \lambda_e^2 \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} g_1(\mathbf{x}_1) g_2(\mathbf{x}_2) \mathrm{e}^{-\lambda_b U(\mathbf{x}_1, \mathbf{x}_2)} d\mathbf{x}_1 d\mathbf{x}_2 \\ &\quad - \lambda_e^2 \int_{\mathbb{R}^2} \int_{\mathbb{R}^2} g_1(\mathbf{x}_1) g_2(\mathbf{x}_2) \mathrm{e}^{-\lambda_b \pi \left(|\mathbf{x}_1|^2 + |\mathbf{x}_2|^2\right)} d\mathbf{x}_1 d\mathbf{x}_2 \end{aligned}$$

$$\mathbb{E}\left[\sum_{\mathbf{x}\in\Phi} g(\mathbf{x})\right] = \lambda \int g(\mathbf{x}) d\mathbf{x},$$

$$\mathrm{Cov}\left(\sum_{\mathbf{x}\in\Phi} g_1(\mathbf{x}), \sum_{\mathbf{x}\in\Phi} g_2(\mathbf{x})\right) = \lambda \int_{\mathbb{R}^2} g_1(\mathbf{x}) g_2(\mathbf{x}) d\mathbf{x}$$

$$\mathrm{Cov}(X, Y) = \mathrm{Cov}(\mathbb{E}[X|\mathcal{Z}], \mathbb{E}[Y|\mathcal{Z}]) + \mathbb{E}[\mathrm{Cov}(X, Y|\mathcal{Z})],$$

for any σ-algebra $\mathcal{Z}$

$$\mathbb{E}[N_o] = \frac{\lambda_e}{\lambda_b},$$
$$\mathbb{E}[L_o] = \frac{\lambda_e}{2\lambda_b^{\frac{3}{2}}},$$

$$\mathrm{Var}(N_o) \approx \frac{\lambda_e}{\lambda_b} + 0.280\,\frac{\lambda_e^2}{\lambda_b^2},$$
$$\mathrm{Var}(L_o) \approx \frac{\lambda_e}{\pi\,\lambda_b^2} + 0.149\,\frac{\lambda_e^2}{\lambda_b^3},$$
$$\mathrm{Cov}(N_o, L_o) \approx 0.190\frac{\lambda_e^2}{\lambda_b^{\frac{5}{2}}} + \frac{\lambda_e}{2\lambda_b^{\frac{3}{2}}}.$$

Hierarchical Constraints

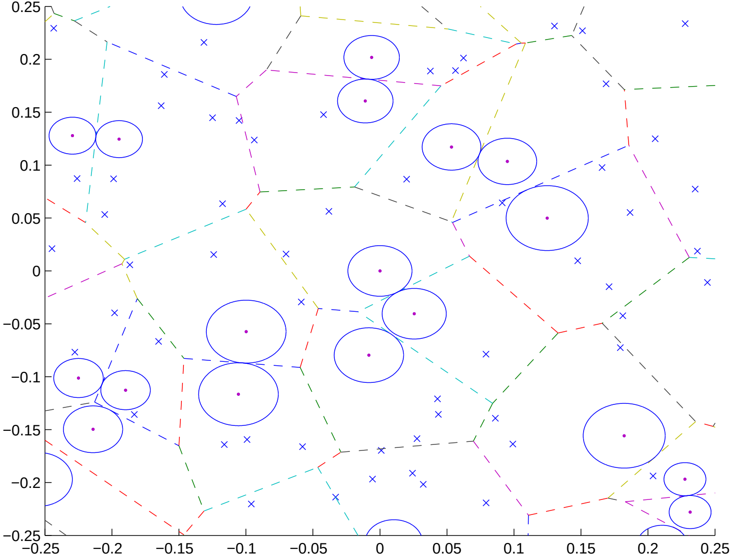
For any measurable function $g : \mathbb{R}^2 \rightarrow \mathbb{R}_+$, define

$$\tilde{\Sigma}_g = \sum_{\mathbf{x} \in \Phi_e} g(\mathbf{x}) \mathbf{1}_{\{\mathbf{x} \in \mathcal{V}_o \cap \mathcal{C}_o\}},$$

where $\mathcal{C}_o$ is a random set.

$$\mathcal{C}_o = \{\mathbf{x} \in \mathbb{R}^2 \ : \ |\mathbf{x}| \geq R_o\},$$

for a non-negative random variable R_o.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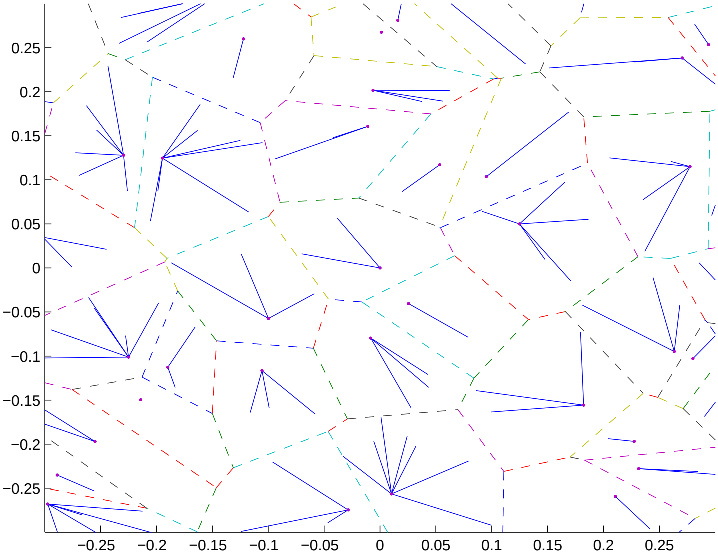
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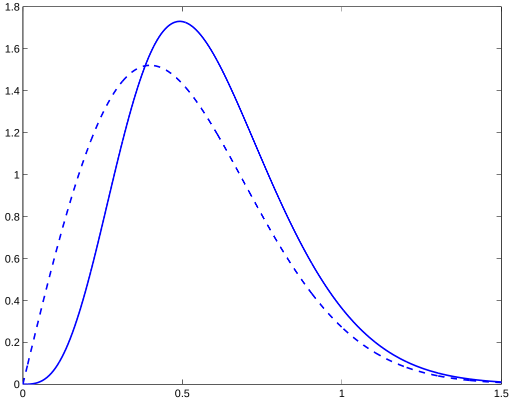
Let R_o be half the distance to the closest neighbor.

$$P(R_o < r) = D(2r) = 1 - \mathrm{e}^{-\lambda_b 4\pi r^2}$$

Branch Length

$$f_{B_h}(x \mid \lambda_b) = \frac{8}{3}\lambda_b \pi x\, \mathrm{e}^{-\lambda_b \pi x^2} \left(1 - \mathrm{e}^{-\lambda_b 3\pi x^2}\right)$$


1.8
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1.2
1
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0.6
0.4
0.2
0
0
0.5
1
1.5

Theorem 3 For any measurable function $g : \mathbb{R}^2 \to \mathbb{R}_+$, we have that

$$\mathbb{E}\left[\tilde{\Sigma}_g\right] = \lambda_e \int_{\mathbb{R}^2} g(\mathbf{x}) \mathrm{e}^{-\lambda_b \pi |\mathbf{x}|^2} \left(1 - \mathrm{e}^{-3\lambda_b \pi |\mathbf{x}|^2}\right) .d\mathbf{x},$$

$$\mathbb{E}[\tilde{N}_o] = \frac{3\lambda_e}{4\lambda_b},$$

$$\mathbb{E}[\tilde{L}_o] = \frac{7\lambda_e}{16\lambda_b^{\frac{3}{2}}}.$$

Theorem 4 For any measurable functions $g_1, g_2 : \mathbb{R}^2 \to \mathbb{R}_+$, we have that

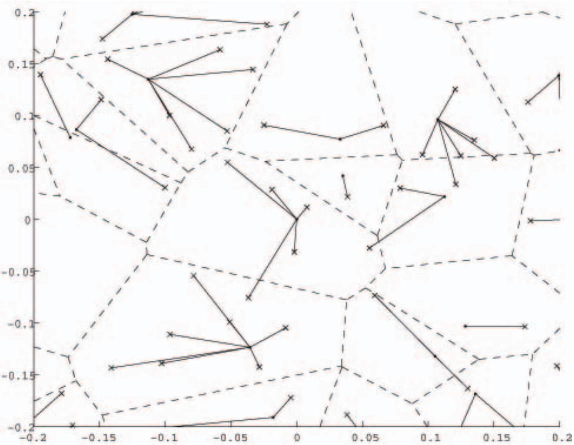
$$\begin{aligned}\mathbb{E}\left[\tilde{\Sigma}_{g_1}\tilde{\Sigma}_{g_2}\right] &= \lambda_e \int_{\mathbb{R}^2} g_1(\mathbf{x})g_2(\mathbf{x})\mathrm{e}^{-\lambda_b \pi |\mathbf{x}|^2}\left(1-\mathrm{e}^{-3\lambda_b\pi|\mathbf{x}|^2}\right)d\mathbf{x} \\ &+\lambda_e^2 \int_{\mathbb{R}^2}\int_{\mathbb{R}^2} g_1(\mathbf{x}_1)g_2(\mathbf{x}_2)\mathrm{e}^{-\lambda_b U(\mathbf{x}_1,\mathbf{x}_2)}d\mathbf{x}_1 d\mathbf{x}_2. \\ &-\lambda_e^2 \iint_{|\mathbf{x}_1|\le|\mathbf{x}_2|} g_1(\mathbf{x}_1)g_2(\mathbf{x}_2)\mathrm{e}^{-\lambda_b V(\mathbf{x}_1,\mathbf{x}_2,2)}d\mathbf{x}_1 d\mathbf{x}_2 \\ &-\lambda_e^2 \iint_{|\mathbf{x}_1|>|\mathbf{x}_2|} g_1(\mathbf{x}_1)g_2(\mathbf{x}_2)\mathrm{e}^{-\lambda_b V(\mathbf{x}_2,\mathbf{x}_1,2)}d\mathbf{x}_1 d\mathbf{x}_2\end{aligned}$$

$$\mathrm{Var}(\tilde{N}_o) \approx \frac{3\lambda_e}{4\lambda_b} + 0.159\frac{\lambda_e^2}{\lambda_b^2},$$

$$\mathrm{Var}(\tilde{L}_o) \approx \frac{15\lambda_e}{16\pi\lambda_b^2} + 0.163\frac{\lambda_e^2}{\lambda_b^3},$$

$$\mathrm{Cov}(\tilde{N}_o, \tilde{L}_o) \approx \frac{7\lambda_e}{16\lambda_b^{\frac{3}{2}}} + 0.251\frac{\lambda_e^2}{\lambda_b^{\frac{5}{2}}}.$$

Soft Boundaries



Branch Length

$$f_{B_s}(r \mid \lambda_b) = \sum_{m=1}^{\infty} f_{B_m}(r \mid \lambda_b) f(m),$$

where

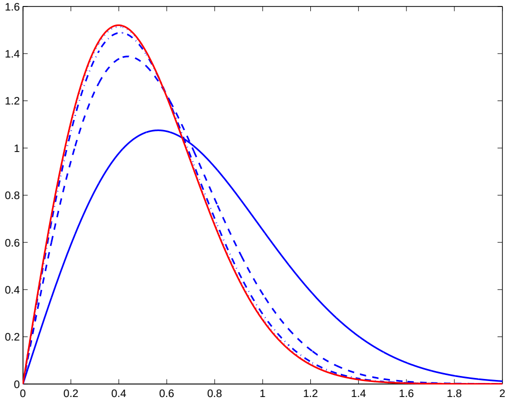
$$f_{B_m}(r|\lambda_b) = \frac{2(\lambda_b \pi r^2)^m}{r\,\Gamma(m)} \mathrm{e}^{-\lambda_b \pi r^2}.$$

Example: If $f(m)$ is given by

$$f(m\,|\,k) = \frac{(k!-1)}{(k!)^m},\ \ m = 1, 2, \ldots \text{ for some } k = 2, 3, \ldots$$

then

$$f_{B_s}(r|\lambda_b, k) = \frac{2\lambda_b \pi (k!-1)}{k!}\, r\, \mathrm{e}^{\left(\frac{1}{k!}-1\right)\lambda_b \pi r^2}.$$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$$\Sigma_g^s = \sum_{\mathbf{x} \in \Phi_e} g(\mathbf{x}) \mathbf{1}_{\{\mathbf{x} \in \mathcal{O}\}} = \sum_{[\mathbf{x};\, m] \in \Phi_e} g(\mathbf{x}) \mathbf{1}_{\{N(\mathbf{x}, o) = m\}},$$

$$\mathbb{E}\left[\sum_{[\mathbf{x};\, m] \in \Psi} f(x, m) \right] = \lambda \int_{\mathbb{R}^2} \int_{\mathbb{M}} f(x, m) M(dm) d\mathbf{x}.$$

$$\mathbb{E}[\Sigma_g^s] = \lambda_e \sum_{m=1}^{\infty} \frac{f_M(m)(\lambda_b \pi)^m}{m!} \int_{\mathbb{R}^2} g(\mathbf{x})|\mathbf{x}|^{2m} \mathrm{e}^{-\lambda_b \pi |\mathbf{x}|^2} d\mathbf{x}.$$

$$\mathbb{E}[N_s] = \frac{\lambda_e}{\lambda_b},$$

$$\mathbb{E}[L_s] = \frac{\lambda_e}{\lambda_b^{\frac{3}{2}} \pi^{\frac{1}{2}}} \sum_{m=1}^{\infty} \frac{f_M(m)\Gamma(m + \frac{3}{2})}{m!}.$$

Future Work

- Fit
- Inference

- 3-dimensional model
- Dynamic