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Constrained confidence partitioning. An innovative technique towards personalized drug treatment

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[1]: Speaker

Overview

I. Introduction

II. Constrained Confidence Partioning

III. Prototypical Results

IV. Conclusion

I. Introduction

Motivating question from medical science partners

- Can you identify (prototypes of) patients for that a specific treatment shows „significant“ different efficacy?
- In any case, a comprehensible (easy) explanation is mandatory!

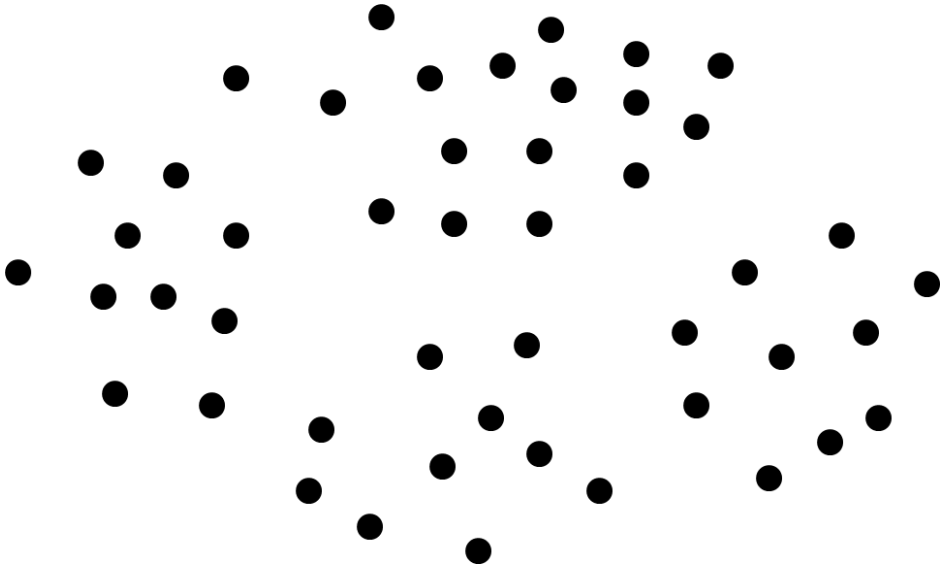
Basic Idea

- After a suitable data transformation find such prototypes by an optimal partitioning of a high-dimensional geometric space.
- Do descriptive, predictive, or prescriptive analytics on the partition.

II. Constrained Confidence Partitioning

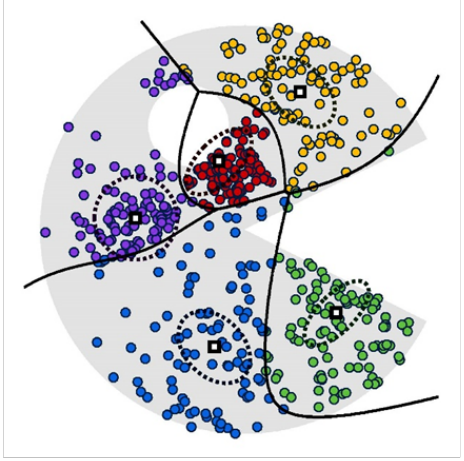
Detecting hidden data structures

- homogeneous clusters
- any dimension
- any number of clusters
- weighted points
- cardinality constraints
- „efficient running time“

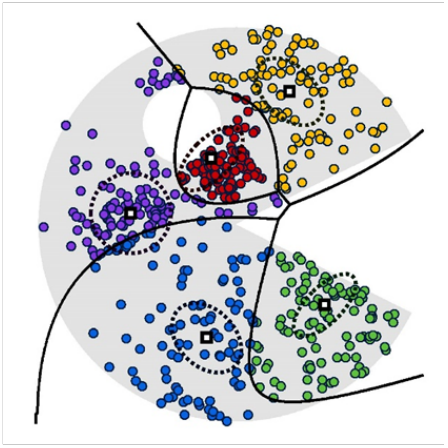


Proximity measures and diagrams

- Proximity measures $\delta_i : 1 \leq i \leq k$
- Cluster definition $P_i := \{x \in \mathbb{R}^n : \delta_i(x) \leq \delta_l(x), 1 \leq l \leq k\}$



$$\delta_i(x) = \sqrt{(s_i - x)^T M_i (s_i - x)}$$



$$\delta_i(x) = (s_i - x)^T M_i (s_i - x)$$

s_i: (given) sites, M_i: sym. pos.-def. matrix

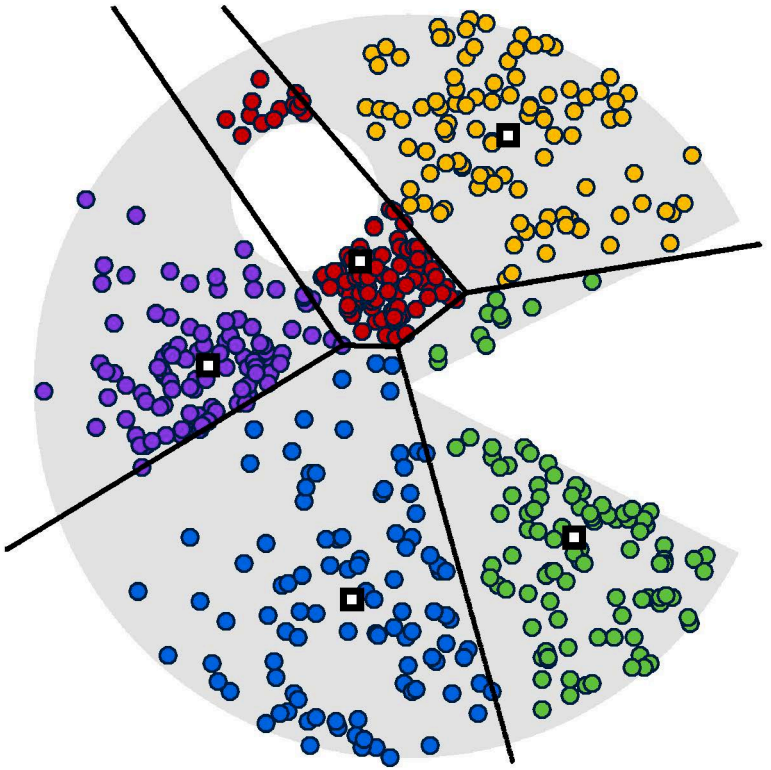
Convex Maximization (non pre-specified sites)

- Power diagram

$$\max \sum_{i=1}^{k} \sum_{j=1}^{k} \kappa_i \kappa_j \| c_i - c_j \|_2^2$$

$$\kappa_i^- \leq w(C_i) \leq \kappa_i^+, 1 \leq i \leq k$$

c_i: virtual center of gravity



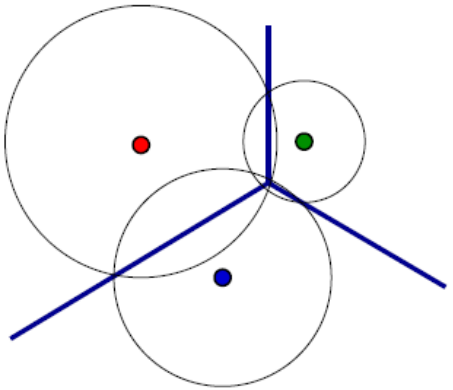
$$\delta_i(x) = \|c_i - x\|_2^2$$

Power Diagram (weighted Voronoi diagram)

- control points $s_1, \dots, s_k \in \mathbb{R}^d$
- weights $w_1, \dots, w_k \in \mathbb{R}$
- Voronoi dissection:

Cell decomposition of $\mathbb{R}^d$ into convex polyhedra $P_1, \dots, P_k$ with

$$P_i = \left\{ x : j \neq i \Longrightarrow \|s_i - x\|_2^2 - w_i \leq \|s_j - x\|_2^2 - w_j \right\}$$



Gravity polytope

- feasible partition $V_1, \dots, V_k$ of points: $V_i \subseteq P_i, 1, \dots, k$
- gravity vector g_c of centers of gravity $c_1, \dots, c_k$:

$$g_c := \begin{pmatrix} c_1 \\ \vdots \\ c_k \end{pmatrix} \in \mathbb{R}^{dk}$$

- gravity polytope Q:

  $Q := \mathrm{conv}(g_c : g_c \text{ is the gravity vector of a feasible partition})$

Results for the gravity polytope

- In the combinatorial case, each extremal clustering (i.e., a vertex of Q) admits a voronoi dissection.

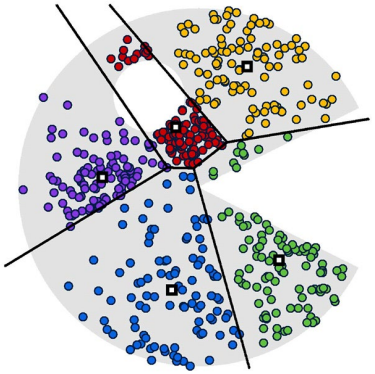
  Barnes, Hoffmann, Rothblum ´92, Aurenhammer, Hoffmann, Aronov ´98

  Br. & Gritzmann ´06, Borgwardt ´10

- ...

- Solving $\max \sum \sum \kappa_i \kappa_j \left\| c_i - c_j \right\|_2^2$ corresponds to Norm-Maximization over gravity polytopes.

  Br. & Gritzmann ´11



Complexity of Norm-Maximization over polytopes

- Approximation error of $\Theta(d/\log d)$ (in general)

  Bárány & Füredi ´89, Kochol ´94

  Br., Gritzmann, Kannan, Klee, Lovász & Simonovits (also for polynomial-time randomized algorithms)

- APX-hardness (even in special cases)

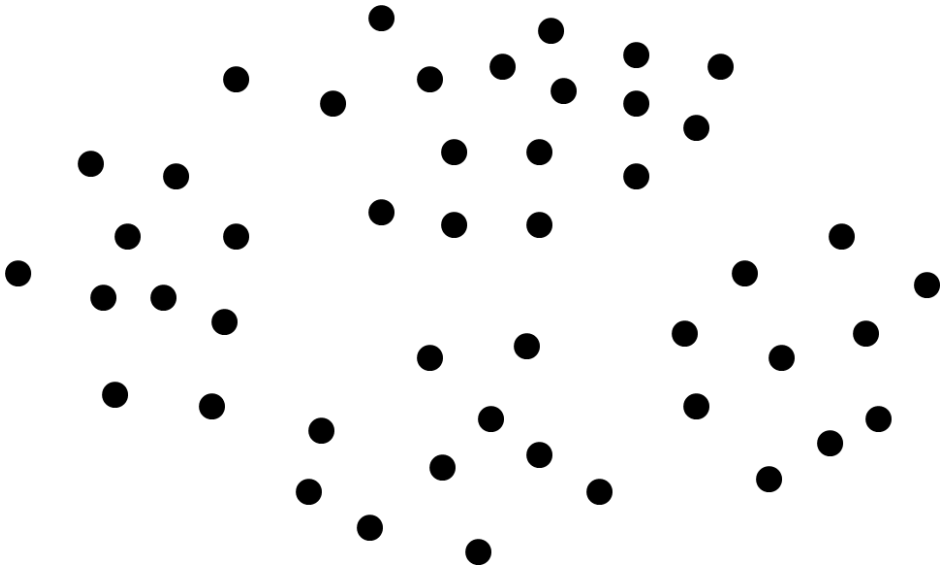
  Br. ´02

- Practical results much more promising!

II. Constrained Confidence Partitioning (revisited)

Detecting hidden data structures

- ✓ homogeneous clusters
- ✓ any dimension
- ✓ any number of clusters
- ✓ weighted points
- ✓ cardinality constraints
- ✓ „efficient running time“



Endpoint oriented data transformation

- General method

  Discrete Radon Transformation (Discrete Tomography)

- Basic Application

  axes parallel x-rays (conditional mean values)

$$\begin{pmatrix} \text{age} \\ \text{recent drug abuse} \\ \text{anxiety disorder} \\ \vdots \end{pmatrix} \Rightarrow \begin{pmatrix} \text{survival time age} \\ \text{survival time recent drug abuse} \\ \text{survival time anxiety disorter} \\ \vdots \end{pmatrix} \in \mathbb{R}^d$$

Sometines necessary: binning & variable selection

III. Prototypical Results

a. From industry: „Hiring bias (?)“

b. From science: New insight into the Catie study

„Hiring bias (?)“

- Baseline:

  Results from multinational randomized control trials do not show overall evidence (only in Europe) for higher efficacy of new drug compared to placebo.

  This is in contrast to expert knowledge from „real-life treatment“ .

- Crucial pairs of patient prototypes detected by c^2p:

  groups HP and HV with high response rate, HP getting placebo, HV verum

  groups LP and LV with low response rate, LP getting placebo, LV verum

Crucial Prototypes

- HV:

  not surprising
- HP:

  mainly young male Americans
- LV:

  mainly „lost to follow ups“ with „last observation carried forward“

  mainly young male Americans
- LP:

  not surprising

A possible explanation (from our partners)

- HP:

  „If I am paid, I have to perform!“

- LV:

  „My doctor does not know me and it is not enough money!“

New insight into the CATIE study

- CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness
- Should compare the effectiveness of older (first available in the 1950s) and newer (available since the 1990s) antipsychotic medications used to treat schizophrenia.
- Is known as the largest, longest (18 month), and most comprehensive independent trial ever done to examine existing therapies for schizophrenia.

Prototypical already known and new results

- Known: Clinical Antipsychotic Trials of Intervention Effectiveness
  - Olanzapine is superior to Ziprasidone
- New: Consider the following two prototypes:

  noADH (No A) No anxiety disorder in the past month,
  (No D) No drug abuse in the past 5 years, and
  (No H) No hospitalization in the past year

  ADH at least one of the above properties
  - Superiority of Olanzapine is even more distinct for group noADH,

    but (very) questionable for ADH

    Schiele, Br., Leucht & Heres ´21

IV. Conclusion

- general approach
- delivers valuable, explainable insight into data (especially by analyzing look-up tables)
- has successfully applied in many fields of application (medicine, insurance, finance, logistics ...)

Final take away