APPLICATION OF THE PYHASSE PROGRAM FEATURES: SENSITIVITY, SIMILARITY, AND SEPARABILITY FOR ENVIRONMENTAL HEALTH DATA

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SUMMARY

It has been evident for decades that many environmental chemicals pose an enormous risk to the environment as well as to humans. There is increasing pressure to intensify the research and to more efficiently evaluate the data on persistent and bioaccumulative chemicals in the environment as well as in human bodies. An appropriate data analysis method is based on the theory of partially ordered sets. The program PyHasse, developed by the third author, provides several features which are useful for gaining information out of the data and drawing conclusions concerning the impact of those chemicals and their prevention. In our data analysis approach we investigated data sets of breast milk samples of women in Denmark and Finland which contained measurable levels of 32 persistent organic pollutants (POPs). Three important features of the PyHasse program are used: The Sensitivity Analysis, the Similarity Analysis and the Separability Analysis. The aim of this discrete mathematical approach is to find differences in the chemicals' contamination between the healthy boys and those boys who were suffering from congenital malformations (cryptorchidism).

***Keywords:** Environmental Health Data, Persistent Organic Pollutants (POPs), Cryptorchidism, Partial Order, PyHasse Program.*

1. INTRODUCTION

Over the last 20 years, endocrine disruption research has shown how chemicals in our environment can profoundly affect development, growth, maturation, and reproduction by mimicking hormones or interacting with hormone receptors. There are many more mechanisms of gene regulation that are potentially susceptible to alteration by environmental influences. The effect of environmental contaminants on health is a major concern because exposure is associated with a number of diseases,

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including cancer, diabetes, and infertility (Edwards and Myers, 2007). Even in a lean person, white adipose tissue (WAT) represents about 15 to 25 % of body weight, and this percentage can increase by more than 50 % in cases of morbidly obese patients. Since about 70 % of the mass of WAT is formed by lipids, this tissue represents a major reservoir for many different lipophilic contaminants. Most of them are persistent organic pollutants (POPs) which are also accumulated in higher trophic levels of the food chain. Thus food, especially fatty fish, meat and milk products, is the main source of human exposure to POPs. The variability of the stored amount of particular POPs in WAT, which can range over several orders of magnitude, depends on dietary exposure and on individual disposition to store these substances. Weight loss results in an increase of their concentration in reduced WAT and their elimination rate is consequently decreased significantly with increasing body fat content (Muellerova and Kopecky, 2007). There is evidence that one of the potential diseases, cryptorchidism (congenital malformation), is caused by chemicals, especially POPs (Persistent Organic Pollutants). The Stockholm Convention is a global treaty to protect human health and the environment from chemicals that remain intact in the environment for long periods, become widely distributed geographically, accumulate in the fatty tissue of humans and wildlife, and have adverse effects to human health or to the environment. Exposure to Persistent Organic Pollutants (POPs) can lead to serious health effects including certain cancers, birth defects, dysfunctional immune and reproductive systems, greater susceptibility to disease and even diminished intelligence. Given their long range transport, no one government acting alone can protect is citizens or its environment from POPs. In response to this global problem, the Stockholm Convention, which was adopted in 2001 and entered into force in 2004, requires Parties to take measures to eliminate or reduce the release of POPs into the environment. The Convention is administered by the United Nations Environment Programme based in Geneva, Switzerland (UNEP, 2011).

A lot of evidence is given that there is a strong relationship between the exposure of women with chemicals and the development of cryptorchidism (malformation of the testis in the male offspring). The association between congenital cryptorchidism and some persistent pesticides in breast milk as a proxy for maternal exposure suggests that testicular descent in the fetus may be adversely affected. A possible human association between maternal exposure to POPs used as pesticides and cryptorchidism among male children has been investigated. These investigations have shown striking differences in semen quality and testicular cancer rate between Denmark and Finland. Since malformation of the testis is a shared risk factor for these conditions, a joint prospective study for the prevalence of congenital cryptorchidism was executed in Denmark (1997-2001) and Finland (1997-1999). These data have already been analysed by classical statistical methods (Damgaard et al., 2006; Shen et al., 2008). The studies suggested an association between congenital cryptorchidism and some persistent organochlorine pesticides present in mothers' breast milk. Thus, prenatal exposure to persistent organochlorine pesticides may adversely affect testicular descent in boys. Our data analysis approach published in 2010 supported this association (Voigt et al., 2010).

The present study, for which PyHasse (a software package for ordinal analysis of data matrices) will be applied, aims at finding a relation between concentrations of chemicals and the appearance of cryptorchidism. The emphasis is laid on the introduction and application of three PyHasse features. For further reading see Brüggemann and Patil (2010; 2011) and Voigt *et al.* (2010).

Generally, we are of the strong opinion that we should intensify the research and furthermore efficiently evaluate the data on persistent and bioaccumulative chemicals in the environment as well as in human bodies. The PyHasse program is one effective way for the data analysis of data on this topic.

2. PYHASSE AND ITS MODULES

The new and innovative software package is that of PyHasse, developed by the third author (Brüggemann and Patil, 2010). Py stands for Python which is used as 'rapid prototyping' programming language. Python belongs to the so-called 'Very High Level Languages' (VHLL) which allows for a high level of abstraction (Muller and Schwarzer, 2007). The concept of 'dictionaries' by which complex relations can efficiently be programmed may be given as an example. Python can freely be downloaded, for instance from http://www.python.org/download, is platform independent and runs on many operating systems. Python has access to many packages either in algebra, in statistics, in graphics, or cloud computing, or even in preparing sound effects, game developments and image processing. Python allows object-oriented programming and is itself modularized to a very high degree. On http://www.pythonology.com/home one finds many more pieces of information. In contrast to WHASSE, the parent software version (Brüggemann and Carlsen, 2006), PyHasse is considered as ''experimental'' software, which is considered as to bridge the gap between professional software and software, exclusively developed in laboratories and in general only applicable by the developer.

It has to be pointed out that the PyHasse software is under constant development. This means that the described modules might be updated in the time between writing the paper and its publication. The software can be acquired by the third author Dr. Rainer Brüggemann.

2.1 *PyHasse Menue (PyHassemenue8)*

PyHasse, aiming at an ordinal analysis of data matrices, is mainly concerned with ranks and order relations. Hence, identification and analysis of partial order relations is a central point in PyHasse. Other features of PyHasse are for instance calculation of Copeland scores (Al-Sharrah, 2011) or the analysis of composite indicators in terms of their constituent attributes.

We start with the main PyHasse menu. Figure 1 gives a screenshot of the main feature.
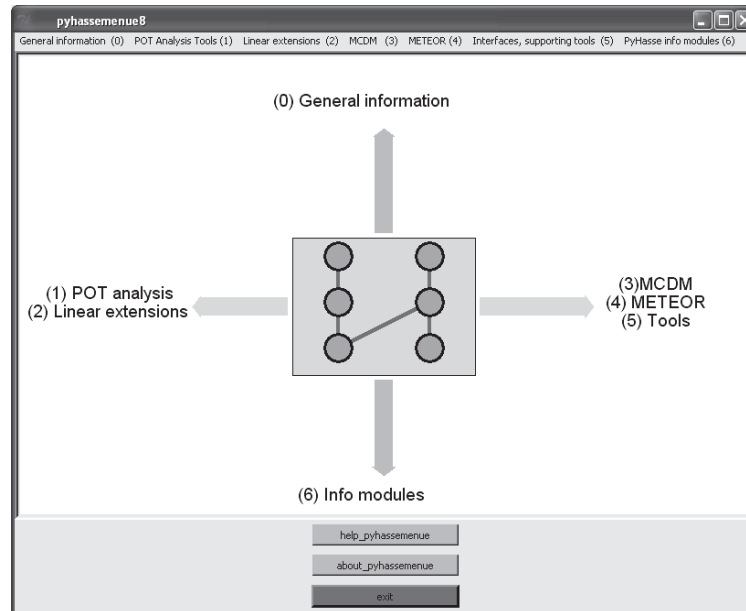
FIGURE 1. - *PyHassemenue8*

In the upper row we find after the general info the button for POT (Partial Order Technique) Analysis Tools.

In the following sections we will explain three of these tools, namely the sensitivity analysis, the similarity analysis, and the separability analysis. We will organize these sections as follows:

Aim of the method: actual name of the module used in PyHasse, a general outline of the method.

- Results in a general sense, without referring to applications within this study and
- Results, used for this study: A short glue what is explained in detail in Section 4.

2.2 *PyHasse: Sensitivity Analysis*

Aim of the method:
Actually there is the module sensitivity_2.py, last modification: August, 2011.

The ordinal analysis of data matrices (rows characterizing the objects and columns their attributes) is based on the product order, therefore it is of interest to identify the influence of each column of the data matrix (the attribute) on the partially ordered sets in terms of order relations. Hence, the task of sensitivity analysis is to find the most important attributes based on the distances of the different posets resulting from eliminating one after another column of the data matrix in comparison to the original poset. (Details see Brüggemann and Patil, 2010; 2011).

Results:

The sensitivity analysis depends on the set of object. Therefore there are two different modi: The global one Sensitivity analysis based on all objects and sensitivity analysis based on single objects: How is an object affected if one of the columns is deleted from the original data matrix. Beyond this there is a partitioning analysis of the attribute set: Based on the sensitivity analysis the set of attributes can be partitioned into two subsets: One with heavy influence on the poset and another one which may be considered as ''fine tuning'' effects, because the sensitivity with respect to these attributes may turn out as being low. The partitioning can be performed by means of the ''ambiguity graph'', which is shown in Figure 2, right hand side.

Results with respect to this study:

In a) the module ''sensitivity'' of PyHasse provides a bar diagram, where the height of each bar, associated with one of the attributes of the analysis (the columns of the data matrix) indicates the impact of this attribute onto the poset (Figure 2). In Figure 2 however, we only are interested in the results of the bar diagram (middle position). On the left hand side of the Hasse diagram is given and one the right hand side the sensitivity diagram of the whole data matrix is displayed and the ambiguity graph is calculated. Here the ambiguity graph changes pretty suddenly the slope. This observation motivates a decomposition of the attribute set, which, however is out of the scope of the paper (details, see Brüggemann and Patil, 2010).
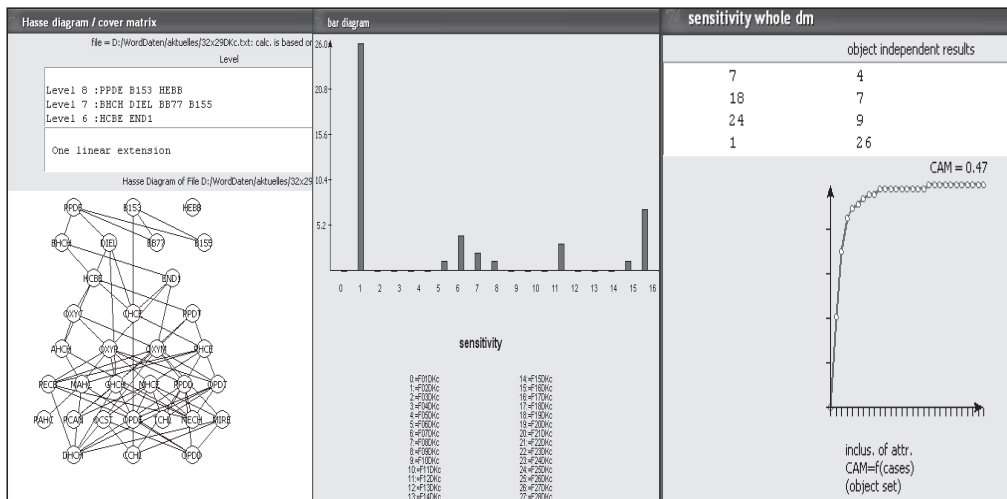

FIGURE 2. - *Sensitivity Analysis with some Sub Features*

The results of the sensitivity analysis will be explained later in Section 4.1.

2.3 *PyHasse: Similarity Analysis*

Aim of the method:

The actual PyHasse module is similarity8.py, the last modification was performed in October, 2011. This PyHasse feature gives the user quantitative information about the similarity of posets of two data sets. The mathematical background can be found e.g. in Voigt and Brüggemann (2010) where this feature is applied on environmental health data of the same origin as in the current paper.

Several computations can be calculated, like "show Hasse diagrams/data matrices", "calculation of similarity", and "bar diagram" which is given for an example in Figure 3. The results are discussed in Section 4.2.
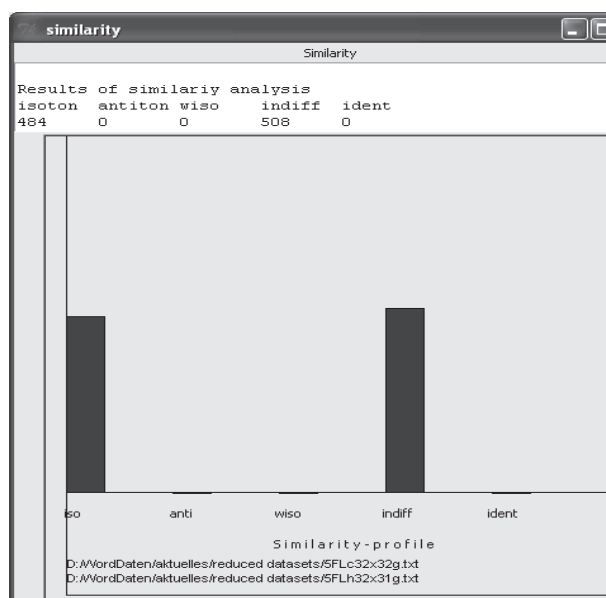

FIGURE 3. - *Similarity Analysis: Bar Diagram FLcrypto / FLhealthy*

Results with respect to this study:

Of most interest is a bar diagram of the type, shown in Figure 3. Taken two samples, one with proven cryptorchidism and one with no effect. How will the position of chemicals within a Hasse diagram be changed when we compare these two samples. More details will be found in Section 4.

2.4 *PyHasse: Separability Analysis*

Aim of the method:

The actual module of PyHasse is last modification December 2010. This module is mainly designed for publications, because all graphics are in black and white. For analyses purposes the colored graphics are better readable, therefore a version sepanal15_coloured.py is provided too.

Two disjoint subsets E_1 and E_2 of the ground set E are by definition separated if $x_1 \in E_1$, $x_2 \in E_2$ implies $x_1 \parallel x_2$, i.e.x_1 and x_2 are not comparable. Now the question is, which attributes are responsible and in which manner for this separation. This task has two aspects:

identify a minimal set of attributes, by which E_1 and E_2 are separated; and what is the orientation of the attributes. I.e. let (x_1,x_2) be a pair of objects, $x_1 \in E_1$ and $x_2 \in E_2$. Let be q_i and q_j attributes which are identified by step a) as responsible for the separation, then we want to know the relations between x_1 and x_2 due to q_i and due to q_j.

Results:

The module sepanal15_3 is one of the most complex programs of PyHasse. Correspondingly it delivers many results:

a) bar diagrams:
    a1) How often q_i is responsible for $x_1 > x_2$, $x_1 \in E_1$, $x_2 \in E_2$;
    a2) How often q_i is responsible for $x_1 < x_2$, $x_1 \in E_1$, $x_2 \in E_2$;
    a3) How often q_i is responsible for $x_1 = x_2$, $x_1 \in E_1$, $x_2 \in E_2$.

b) Generating a ''tripartite graph'' and its analysis. The tripartite graph is obtained as follows: Let be (x_1,x_2) a pair of objects with $x_1 \in E_1$ and $x_2 \in E_2$, E_1, E_2, disjoint object subsets. We call the attribute set IB (information base) and consider $IB*IB*(E_1*E_2)$. The elements of IB as well as those of (E_1*E_2) are considered as vertices of a graph. The vertex q_i (i=1,...,$|IB|$) of one IB is connected with (x_1,x_2), if $q_i(x_1) > q_i(x_2)$, the vertex q_j (j=1,...,$|IB|$) of the other IB is connected with (x_1,x_2) if $q_j(x_1) < q_j(x_2)$. Provided a suitable graphical arrangement - the so constructed tripartite graph - allows answers to the question given above. Sepanal15_3.py and sepanal15_coloured.py allow not only to study parts of the tripartite graph, which are of actual interest, but also to find a minimal set of attributes explaining the separation.

c) The separated subsets E_1 and E_2 are most often contextually defined. Then it cannot be excluded that the orientation of the attributes is changing if different pairs (x_1,x_2) are defined. The changing of the attributes orientation for different pairs $(x_1,x_2) \in E_1 * E_2$ is called their ''mixing character'' and is given as a result of sepanal15_3,py and sepanal15_coloured, respectively.

More details, see Brüggemann and Voigt (2011).

Results with respect to this study:

In this study we concentrate ourselves on results a), i.e. on the bar diagrams, informing about the orientation of the attributes, given two separated subsets. The aspects b) and c) are not considered here.

The application is demonstrated in Section 4. In order to receive some preliminary impression, in Figure 4 a part of the graphical user interfaces of sepanal15_coloured.py is shown and two bar diagrams are presented, where each attribute (breast milk sample of an anonymous women) is represented by a bar, showing the percentage of its contribution to $x_1 > x_2$ or $x_1 < x_2$. (Note, for the sake of simplicity we write x and y instead of x_1 and x_2.)
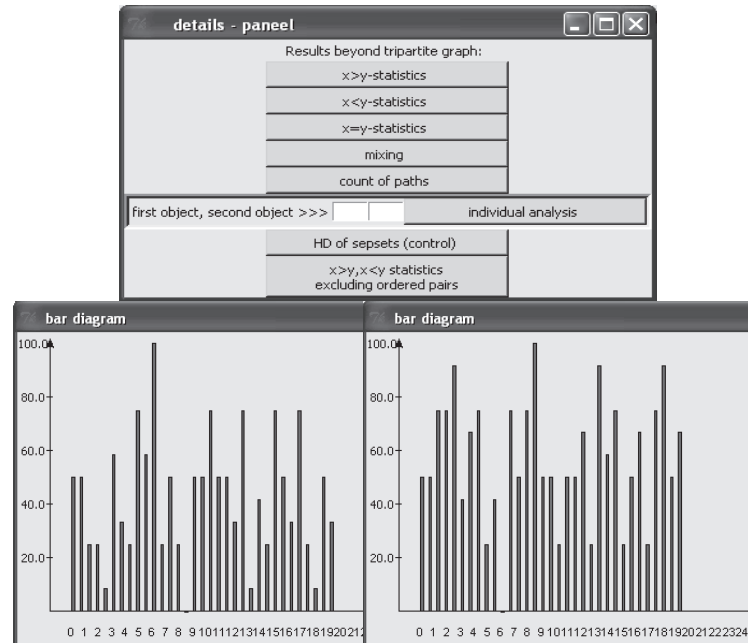
FIGURE 4. - *Separabilityy Analysis :x > y – statistics lhs and x < y – statistics rhs*

3. ENVIRONMENTAL HEALTH DATA SETS

Environmental health is the branch of public health that is concerned with all aspects of the natural and built environment that may affect human health. Other terms that concern or refer to the discipline of environmental health include environmental public health and environmental health and protection. Environmental health is defined by the World Health Organization as:

''Those aspects of the human health and disease that are determined by factors in the environment''. It also refers to the theory and practice of assessing and controlling factors in the environment that can potentially affect health (WIKIPEDIA, 2011). Hence our studies must be regarded as environmental health data analyses.

Studies were performed in Denmark (1997-2001) and Finland (1997-1999). Association between cryptorchidism and the occurrence of environmental chemicals in breast milk has to be evaluated (Damgaard *et al.*, 2006; Shen *et al.*, 2008).

In our current data analysis approach we investigated data sets of breast milk samples of women in Denmark and Finland which contained measurable levels of 32 persistent organic pollutants (POPs). We have to evaluate a data matrix with 32 rows (chemicals, as the objects) and 65 columns (breast milk samples of 65 anonymous women, as the attributes). Out of the 65 samples (complete data matrix) in each country we can select two different subsets according to healthy boys and boys with cryptorchidism. Note that basically the transposed data matrix would be of high interest too. What is the ranking of the women, due to their level of chemicals' concentration? However, as we do not have any background information about the women, this transposed data matrix is not studied here.

In Table 1 we can see the 32 chemicals with their abbreviation and CAS-numbers.

TABLE 1. - *32 POPs detected in breast milk samples*

Nr.	Acronym	Name	CAS-Number
01	PECB	Pentachlorobenzene	608-93-5
02	AHCH	alpha-Hexachlorcyclohexane	319-84-6
03	PAHC	+ Enantiomer alpha-Hexachlorcyclohexane	
04	MAHC	- Enantiomer alpha-Hexachlorcyclohexane	
05	BHCH	beta-Hexachlorcyclohexane	319-85-7
06	GHCH	gamma-Hexachlorcyclohexane	58-89-9
07	DHCH	delta-Hexachlorcyclohexane	319-86-8
08	PCAN	Pentachloroanisole	1825-21-4
09	HCBE	Hexachlorobenzene	118-74-1
10	OCST	Octachlorostyrene	29082-74-4
11	OXYC	Oxychlordane	27304-13-8
12	OXYP	+ Enantiomer Oxychlordane	
13	OXYM	- Enantiomer Oxychlordane	
14	CHCE	cis-Heptachloroepoxide	1024-57-3
15	PHCE	+ Enantiomer cis- Heptachloroepoxide	
16	MHCE	- Enantiomer cis- Heptachloroepoxide	
17	OPDE	o, p'-Dichlordiphenyldichlorethene	3424-82-6
18	PPDE	p, p'-Dichlordiphenyldichlorethene	72-55-9
19	TCHL	trans-Chlordane	5103-74-2
20	CCHL	cis-Chlordane	5103-71-9
21	END1	Endosulfan-1	959-98-8
22	PPDD	p, p'-Dichlordiphenyldichlorethane	72-54-8
23	OPDD	o, p'-Dichlordiphenyldichlorethane	53-19-0
24	DIEL	Dieldrin	60-57-1
25	OPDT	o, p'-Dichlordiphenyltrichlorethane	789-02-6
26	PPDT	p, p'-Dichlordiphenyltrichlorethane	50-29-3
27	MECH	Methoxychlor	72-43-5
28	MIRE	Mirex	2385-85-5
29	BB77	33'44'-BB	40088-45-7
30	B155	22'44'66'-BB	36355-01-8
31	B153	22'44'55'-BB	
32	HEBB	Hexabromobenzene	87-82-1

The chemicals have already been subject to a data evaluation approach using partial order technique (Voigt *et al*., 2011). The ground set *E* comprises 32 chemicals (elements to be compared), the information base IB, i.e. the set of attributes, 65 breast milk samples in Denmark respectively Finland. Unfortunately no information on the attributes like age, weight, work situation, home situation, etc. is available.

We will perform three different analysis steps:

1. Sensitivity: Find the most important attributes and leave them out for further data analyses of the residual data matrix.

2. Similarity: Check two files (e.g. Danish versus Finnish data sets or cryptorchidism vs. healthy).

3. Separability: Subsets of E may consist of elements which are not comparable. Often these subsets are chemicals having common chemical structures. The Separability module of PyHasse intends to find those attributes which are mainly responsible for the observed incomparability.

4. PYHASSE FEATURES APPLIED ON DESCRIBED DATA

4.1 *PyHasse: Sensitivity Analysis*

In order to demonstrate the sensitivity analysis by which we want to identify the most important attributes, we take a subset of above mentioned data matrices into consideration, namely 32 chemicals x 29 cryptorchidism data in Denmark. Taking a look at the middle picture in Figure 2 it is demonstrated that one attribute (F02DKc) is the most important one. Leaving out that very attribute we receive a different Hasse diagram as shown in Figure 5 rhs. In Figure 5 lhs the Hasse diagram of the complete data matrix namely 32x29 is given (lhs). The incomparabilities figures, U, are given in both diagrams.

The sample F02DKc must have high levels of chemicals' concentrations, where most other samples have low values as it has the highest impact on the Hasse diagram. The lack of background data hampers a deepened analysis. One possibility is to consider samples of high impact onto the partially ordered set as outliers and to leave them out.
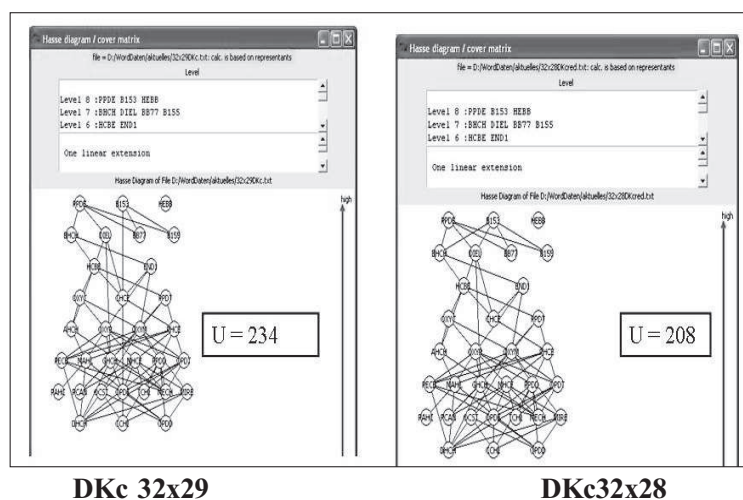

DKc 32x29   DKc32x28

FIGURE 5. - *Hasse Diagram before (lhs) and after (rhs) Sensitivity Analysis*

4.2 *PyHasse: Similarity Analysis*

For this type of analysis we calculate the similarity of cryptorchidism data and healthy data in Finland. The two data matrices 32 chemicals x 29 boys suffering from cryptorchidism and 32 chemicals x 36 healthy boys are looked upon. In Figure 3 it is shown that there are 490 isotone relations and 502 indifferent relations. Most important are the entries like $>>$ or $<<$, which are counting the "isotone" character of both partial orders. The following combinations: $<\|, >\|, \|>,\|<$, $=\|, \|=$ or $\| \|$ are considered as ''indifferent''. Whereas the isotone relations demonstrate a high degree of similarity of the two data sets, the indifferent relations indicate combinations of comparabilities of one Hasse diagram with incomparabilities of the other one. It is striking that there is no contribution to 'antitone', i.e. there is no pair of objects, where for a $>$-relation for instance in the data set of FL, crypto a $<$-relation is found in FL, healthy. I.e. we find:

Sample Finland, cryptorchidism: If the concentration of a chemical A with respect to all woman is greater (or equal) the concentrations of chemical B then there is no case in the sample Finland, healthy contradicting A > B. See also Voigt *et al.* (2010).

It can be concluded from this performed similarity analysis that there exist differences in the two Hasse diagrams but no large ones.

4.3 *PyHasse: Separability Analysis*

In this data analysis step we take a look at different chemical groups. The 32 chemicals listed in Table 2 are differently structured. First we have many chlorinated and several brominated compounds. Then the chemicals can be distinguished by being aromatic or not. That is the reason why we define structural groups of the chemicals for the separability analysis.

A structure classification is performed with the following four structure elements.

Cl	yes	no
Br	yes	no
Aromatic	yes	no
Alkyl	yes	no

The score 0 is attributed to ''no'' whereas the score 1 to ''yes''. We identify four different structure classes. For demonstration the aromatic chlorinated (8 chemicals) and the aromatic brominated compounds (4 chemicals) are taken into account. In this example we analyze the Finnish cryptorchidism and the Finnish healthy data. The results of the separability analysis are given in Figure 6.

Furthermore, we take a look at the x < y statistics as well as the x > y statistics in Figure 6. We take a look at the x < y statistics as well as the x > y statistics in Figure 6. From the bar diagrams we find that the following attributes have the hi-

ghest impact on the separation (highest bars). The following attributes have the highest impact on the separation:

FLc: F27FLc   x>y
FLc: F32FLc   x<y
FLh: F37FLh   x>y
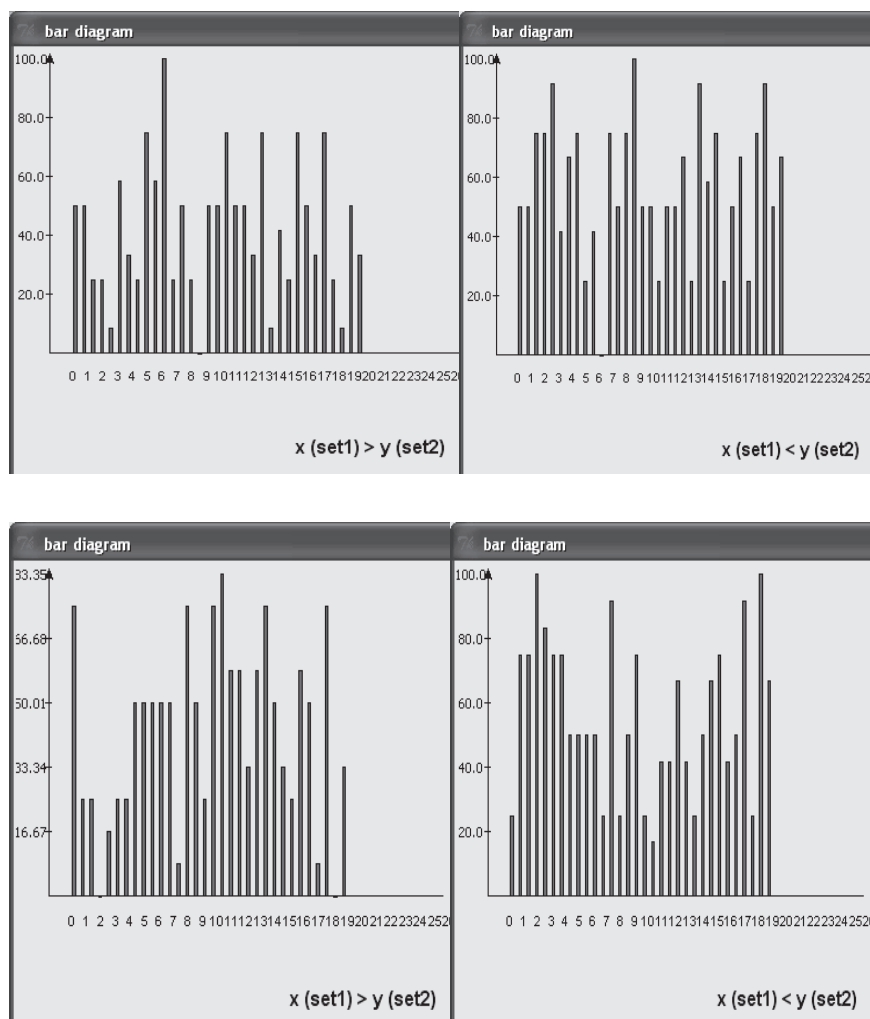FLh: F04FLh, F62FLh   x<y

FIGURE 6. - *Bar Diagram of Separability Analyses, FLc (above), FLh (below) (Note the different scale for the ordinate of bottom, left bar diagram)*

In both the Finnish cryptorchidism data as well as the Finnish healthy data there is one attribute (in the case of FLh two attributes) which separated the aromatic chlorinated from the aromatic brominated compounds the most. It is striking that for the main contribution to the separation of chloro aromatics and bromo aromatics in case

of the healthy system other samples are responsible than in the case of cryptorchidism. Test with other chemical structures should be performed to trace back which different samples are behaving in the same different way.

5. SUMMARY AND CONCLUSIONS

Data matrices which comprise environmental health data, like e.g. the current example of breast milk samples containing 32 chemicals, some of which are healthy and others suffer from cryptorchidism, are often complex in the way that no further information is given on the attribute side. In this case we do not know anything about the women like age, habits, housing, etc. That is the reason why some of the described PyHasse software features which give some more insight into the attribute side are extremely helpful. The sensitivity analysis is a powerful tool to detect the most important attribute(s). In our example of the Danish cryptorchidism data set it is F02DKc. This means that when leaving out this attribute we receive a different Hasse diagram. The possibility of a classification according to chemical structures (chlorinated against brominated aromatic compounds) of the chemicals followed by the separability analysis calculated those attributes which separate the two structure groups in our example chlorinated aromatic compounds from brominated aromatic compounds. We see that in the case of cryptorchidism other samples are leading to incomparabilities than in the case of healthy samples. Hence differences in cryptorchidism/healthy data sets are shown. Furthermore, similarity analyses like comparing the data sets of healthy and cryptorchidism give further insight into environmental health data sets, namely that the uptake mechanism of chemicals seem to be independent from the state (cryptorchidism/healthy). It can be demonstrated that the cryptorchidism differ from the healthy data sets in Finland by a high number of indifferent relations.

In this paper we put the emphasis on the demonstration of PyHasse features. It is exemplified by the features similarity and separability analysis how the two cryptorchidism and healthy data sets differ. The results are just examples which can by no means give a complete insight into the data analysis of Danish and Finnish data sets mentioned above.

From a statistical point of view one of the main needs for a further development of an ordinal analysis of data matrices is the definition of suitable test statistics. For example how sure we can be that one sample has the highest impact on the partially ordered set. One of the first steps of an appropriate development will be simulation studies. Research studies will be performed in this direction in the near future.

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