# The Degree of Order Determined by Local Conditional Entropy: A New Technique to Assess Osteoporotic Changes of Trabecular Networks

Wolfram Timm[a], Claus-C. Glüer[a], and Gerald Sommer[b]

[a]Medical Physics of the Diagnostic Radiology, University Hospital Schleswig-Holstein, Michaelisstr. 9, 24105 Kiel, Germany
[b]Christian-Albrechts-Universität zu Kiel, Institut für Informatik und Praktische Mathematik, Christian-Albrechts-Platz 4, 24118 Kiel, Germany

## ABSTRACT

Trabecular networks of cancellous bone show complex and stochastic characteristics, which have to be modelled in an adequate way to determine pathological changes of the network induced by osteoporosis. The analysis of complexity may be handled by the use of the Markov Theory, which is based on local interactions of a set of elements and thus can be applied to trabecular networks. The conditional entropy which is investigated as a potential measure of complexity, estimates the order of a structure and thus provides a means for classification of healthy versus osteoporotic bone structures. Since the conditional entropy is based on transition probabilities, stochastic characteristics are modelled, too. From a set of 29 female human vertebra T12, classified into two groups of 18 non-osteoporotic and 11 osteoporotic vertebrae axial biopsies were excised from the centre of the vertebral body. A digital model of the trabecular network was extracted with a Micro-CT device (FanBeam Microscope, Stratec, Pforzheim, Germany). Transition probabilities between neighboured voxels were coded as a set of 18 symbols describing the local dimension of a voxel and its relationship to its neighbours within a certain distance. A tree graph of the symbolic transitions coded the transition probabilities and founded a basis for the calculation of the local conditional entropy as a measure of order. The estimated local entropy for a distance at and above 10 voxels showed significantly higher values for the non-osteoporotic subjects than for the osteoporotic ones. This difference indicates, that non-osteoporotic trabecular networks show a higher degree of disorder compared to the osteoporotic ones.

**Keywords:** Trabecular networks, entropy, complexity, osteoporosis, classification

## 1. INTRODUCTION

As all bones, vertebrae are subject to changes with regard to age and diseases like osteoporosis. Bones are described by two main characteristics: bone mineral density (BMD) and architecture. Since bone density can explain up to 83% of the variation in mechanical properties of machined specimens of vertebrae,[1] knowledge about the structural aspects of the way how bone material is arranged may be important in terms of explaining bone integrity. Additionally, the ability to determine pathologic changes of the trabecular network of human vertebrae may allow early detection as well as monitoring the progression of diseases like osteoporosis.

There are several approaches to describe structural properties.[2] For example, direct measures of bone morphometry of cancellous bone are the trabecular number (Tb.N), the trabecular separation (Tb.Sp) or the trabecular thickness (Tb.Th). An example of a structural parameter of a higher order is the degree of anisotropy (DA), which is a measure of the alignment of trabecular connections. While the former standard parameters (Tb.N, Tb.Sp, Tb.Th) are calculated as mean values of a distribution, the parameter DA is a more complex measure by not only averaging but combining the information from the trabecular network within a certain distance.

Further author information: (Send correspondence to Wolfram Timm.)
Wolfram Timm: E-mail: mail@wolfram-timm.de, Telephone: +49 431 597 3156, Webpage: www.uni-kiel.de/radiologie/medphys



Medical Imaging 2004: Image Processing, edited by J. Michael Fitzpatrick, Milan Sonka, Proceedings of SPIE Vol. 5370 (SPIE, Bellingham, WA, 2004)
1605-7422/04/$15 doi: 10.1117/12.535218

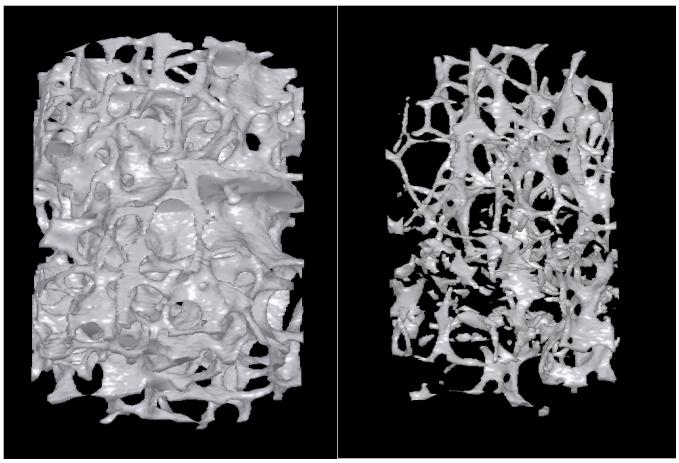

**Figure 1.** Two examples of trabecular networks: The left side shows a bone biopsy with a healthy network, the right side contains an osteoporotic network with a lower number of trabeculae compared to the left one.

Simple parameters may not reflect the pathologic changes of the complex properties of trabecular networks: These networks consist of multiple osseous connections of mainly two primitives: plate like and rod like trabecular elements (see figure 1). Being build of a set of primitives which are connected to each other, the connections of trabecular networks represent interactions of primitives. Since multiple interactions of a set of elements can form a complex system, we study the application of characteristics of complex systems to trabecular networks.

Beside the complexity of trabecular networks, a second aspect has to be taken into account: The stochastic nature which is inherent to natural objects is reflected in the kind of combination of osseous connections: It is well known that the orientation of the trabeculae is influenced by trajectories defined by forces running through the bone. Since a vertebra is mainly exposed vertical forces, within a vertebra two main orientations of the trabeculae can be found: horizontal ones which bear the main load and vertical ones which stabilize the horizontal trabeculae. Since a vertebra is a biological system with multiple stochastic impacts, not only these two main directions can be found, furthermore a mixture of several kinds of directions and connections of trabeculae build the network (see figure 1). Thus, the deterministic part of the trabecular network is modulated by stochastic impacts. This inherent stochastic nature of cancellous bone which is influenced by various physiological as well as pathological factors has to be represented by an adequate mathematical model. Within the framework of *Markov Processes* probability graphs model systems of elements, whose characteristics are dependent only on their neighbours.[3] This breaks down the curse of complex interactions while preserving stochastic characteristics and can be justified by mechanical considerations: The force a single trabecula is exposed is determined solely by the neighboured trabeculae connected to it.

A possible characterisation of differences between healthy and osteoporotic networks is the measure of order or disorder of trabecular networks. Based on the amount of information found in the network structure, the *entropy* of this structure can be calculated,[4] and the *Complexity Theory* gives the method to determine the degree of order or disorder based on entropy.[5] Specifically, the *conditional entropy* models the local interactions found between trabeculae or - a level of resolution down - between voxels, and thus incorporates the second aspect of stochastics into the method investigated in this study. Since computations of conditional entropy are based on symbolic coded structures, a transformation of the continuous valued measurements of the trabecular networks to a discrete valued description symbolic has to be performed.

The application of the conditional entropy enables the investigation of the main hypothesis of this work, which states, that an osteoporotic trabecular network of a human vertebra shows a lower amount of Entropy and thus a higher degree of order than a healthy one.

## 2. METHODS

After specifying the material used in this study a survey over the techniques for obtaining and evaluating an adequate discrete representation of the measured bone biopsies is given now:

### 2.1. Material

A set of 29 female human vertebra T12 without any fractures was classified by an experienced radiologist into two groups of 18 non-osteoporotic and 11 osteoporotic vertebrae. If a vertebra was obtained from a spine which showed an osteoporotic fracture on another vertebra, it was assigned to the osteoporotic group, otherwise to the non-osteoporotic group. The donators of the vertebra of the osteoporotic group had a mean age of 83.18 (+/- 6.98) years, while the mean age for the non-osteoporotic group was 81.61 (+/- 7.2) years. The difference between the age of the groups was not significant. The mean of the bone mineral density (BMD) of the osteoporotic vertebrae was 56.03 (+/- 25.05) $mg/cm^3$. The mean BMD for the non-osteoporotic group was 58.92 (+/- 24.82) $mg/cm^3$. Again, the difference of bone mineral density between the two groups was not significant.

To extract a model of the trabecular network from a human vertebra in vitro, from each vertebra a central biopsy of 8mm diameter and 10 mm length was obtained. Scanning each biopsy with a Micro-CT (FanBeam Microscope, Stratec, Pforzheim, Germany) resulted in a dataset of 512 x 512 x 1000 isotropic voxels of 25 micrometers side length. This measurement assigned each voxel a continuous representation of the corresponding density of the biopsy.

### 2.2. Mapping the voxel space to a symbolic space

To assess measures of complexity a symbolic representation of the trabecular network is needed. This can be achieved by performing a discretisation of the continuous values of the trabecular network using the values of the voxels and their neighbourships. The following four steps are used to map the continuous valued voxel space to the discrete valued symbolic representation:

1. Binarisation
2. Calculating the local dimension of a voxel
3. Exclusion of ambiguities when detecting relationships between voxels
4. Extraction of symbolic sequences out of the 3D-volume.

#### Binarisation

The first step towards a symbolic description of the trabecular network was a classification of the voxelspace into two types of voxels: *bone* and *marrow*. Since the bone biopsies were measured with a high resolution of 25 $\mu$m, a high contrast between bone and marrow were achieved. As a result, the classification into bone and marrow voxels could be done by applying fixed threshold to the continuous valued voxels.

#### Local dimension

Secondly, a refinement of the classification of the bone and marrow voxels into three categories was performed. For each voxel of the type bone the local dimension was calculated (see figure 2). This was achieved by a technique which was used by Bruske[6]: For each voxel, the set of relative vectors to its neighbour voxel of the type bone within a distance of five voxels was determined. Based on this set $A^T = (v_1, ..., v_n)$ a *Local Principal Component Analysis* (LPCA) was performed by calculating the set of eigenvalues $\mu_i$ of the covariance matrix $\sigma = \frac{1}{N} A^T A$. To assess the local dimension of a voxel, the number of eigenvalues which fulfill the criterion from Fukunaga et. al.[7] was used. This criterion regards an eigenvalue as significant, if the equation

$$\frac{\mu_i}{max\mu_j} > a \tag{1}$$

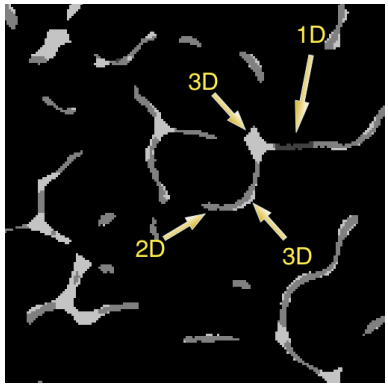


**Figure 2.** This slice through the 3D volume shows the classified trabecular network. The black region represents marrow, while the different gray levels correspond to the three dimensions (dark gray: 1D, the medium gray 2D, light gray: 3D)

is fulfilled. Experiments showed that a value of a=5 lead to reasonable classifications of the local dimension. This classification founded an estimation of the role a single voxel plays in the framework of the trabecular network: A dimension of one is likely to corresponded to a voxel of a rod like trabecula, a dimension of two may correspond to a plate like type, and a dimension of three belongs to a voxel of a junction type. Of course, the set of voxels of a trabecular network cannot be partitioned into these strict cases, since usually mixtures of these three types are found.

The preceding steps of binarisation and calculation of the local dimension transformed the continuous valued volume of the trabecular network into a discrete valued volume of the types:

- marrow
- bone with assigned local dimension of 1
- bone with assigned local dimension of 2
- bone with assigned local dimension of 3

Thus, the voxels as well as the relationships between neighboured voxels of the measured volume were described on a symbolic level.

### Removal of ambiguities

Thirdly, due to the cylindrical shape of the biopsy the set of distinguishable neighbourhood relations has to be determined. In our case, a rotation of the cylindrical biopsy around its main axis is not detectable. Additionally, the orientation of the biopsy upwards or downwards is not distinguishable (see figure 3). In consequence, the only relationships between neighboured voxels which can be taken into account are the vertical and the horizontal direction. Thus, all possible horizontal directions from a voxel to its neighbours are combined to the *horizontal class h*. Similarly, the directions upwards and downwards build the *vertical class v* of neighbourhoods.

### Symbolic sequences of a 3D-structure

The classification of the bone voxels into three classes of dimension on the one side as well as the neighbour relationships of the type *horizontal* and *vertical* on the other side are sufficient to build sequences of voxel relationships on a symbolic level: Considering a bone voxel $v_1$ with an assigned local dimension of 3 and its vertically neighboured bone voxel $v_2$ with an assigned local dimension of 2, we can write this relationship as the symbolic code $v32$. More generally, all relationships between neighboured voxels can be written by an symbolic code out of the set

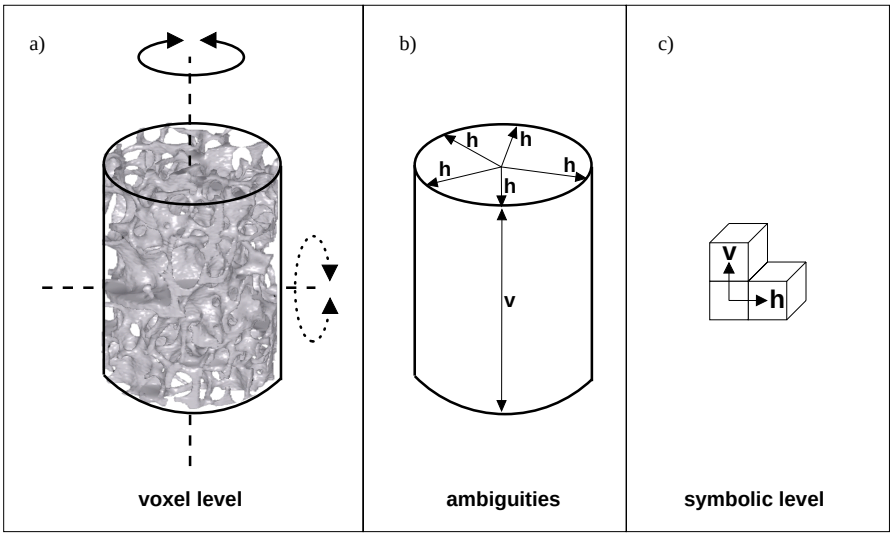


**Figure 3.** a) Due to the cylindrical shape of the biopsies a rotation along the main axis as well as the up- and down side cannot be distinguished. b) As a consequence, all horizontal directions are combined to the horizontal class $h$, and the directions upwards and downwards builds the vertical class $v$. c) Thus, the resulting symbolic representations of distinguishable neighbourhood relations consists of the two symbols $v$ and $h$.

$$A = \{v11, v12, v13, v21, \ldots, v33, h11, h12, h13, \ldots, h33\} \tag{2}$$

Based on this alphabet $A$ with its 18 symbolic descriptions of voxel transitions, a set of symbolic sequences of length $n$ is defined as follows:

$$A^n = \{(c_1, \ldots, c_n) | c_i \in A, i \in \{1, \ldots, n\}\} \tag{3}$$

In order to obtain the alphabet $A^n$, for each biopsy a graph of transition probabilities was build (see figure 4). The sequences of transitions between the voxels were determined by recursively finding all possible symbolic sequences of transitions from a junction type voxel (a voxel with assigned dimension of 3) to neighboured bone voxels within a certain distance. Each node of the resulting tree coded a voxel of a certain type, and each edge of the tree coded the transition probability of the source voxel to a target voxel with a certain dimension and direction. This graph of conditional transition probabilities was suitable for calculating the locally bounded conditional entropy of the underlying trabecular network as a measure of order. The function of the conditional entropy over a distance of two to eighteen voxels was calculated and compared with regard to the osteoporotic and non-osteoporotic vertebrae.

As specified in section 2.2 the local dimension assigned to each voxel of type bone represents the dimension of the local volume (all voxels within a distance of 5) around each voxel. This classification enables the extraction of transitions from voxels to their neighbours while collecting the direction (*horizontal* or *vertical*) as well as the local dimension of a voxel and its neighbour. Doing this, a sequence of transitions defines a sequence of symbolic descriptions of these transitions (see figure 4).

## 2.3. Calculation of the conditional entropy

The basic hypothesis of this work, a higher degree of order of an osteoporotic trabecular network of a human vertebra compared to a healthy vertebra can be tested using the approach of conditional entropy. This technique

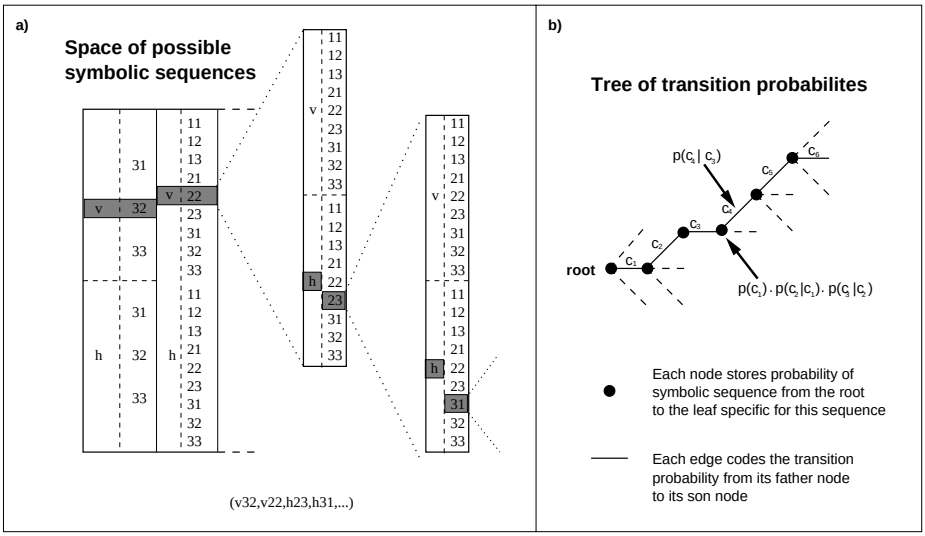


**Figure 4.** a) Sequence of neighboured voxel relationships taken from the space of transition probabilities between classified voxels. b) Tree of probabilities: Transition probabilities are stored in the edges, while probabilities of sequences (and all prefixes) are stored in the nodes.

is a tool for the classification of a structure between the two extremes of a purely random structure and a completely ordered one. The basic idea is to ask, whether a given structure $(c_1, ..., c_n)$, consisting of letters $c_i$ of an alphabet $A$ gives some hint for the extension $(c_{n+1}, c_{n+2}, ...)$ of this sequence, or if this extension is independent of the prefix $(c_1, ..., c_n)$. In the following section two examples of the aforementioned extremal structures are given:

### Nondeterminism and order: Two extremes in the space of predictability

A system which shows nondeterministic characteristics can be assigned to a state between the two extremes of a random or an ordered system. Now two simple examples of these two extremes are given: The first one consists of a purely random structure, where each subsequence is independent from its prefix. This is the one-dimensional Bernoulli Sequence (see figure 5): Each letter $c_i$ of the sequence $(c_1, ..., c_n)$ is drawn independently with regard to certain probability distributions $p(c_1), ..., p(c_n)$ and subsequently concatenated to each other. For example the sequence 0101011100100100101 is an example for such a Bernoulli sequence. The probability for an letter $c_{k+1}$ as an extension of the sequence $(c_1, \ldots, c_k)$ is given by the equation

$$p(c_{k+1}|(c_1, \ldots, c_k)) = p(c_{k+1}) \tag{4}$$

The second example is the counterpart of a random structure. It is a completely ordered, periodic sequence of letters $(c_1, ..., c_n)$ with the condition $c_i = c_j, j = i + t$ for some fixed period length $t$. A trivial example with a period of $t = 3$ is *abcabcabc...* (see figure 5). Within this sequence, all future extensions of a prefix are determined, if at least three letters are known: From any subsequence $(c_i, c_{i+1}, c_{i+1}) \in A^3$ the letter $c_{i+3}$ is known as letter $c_i$ with probability

$$p(c_{i+3} = c_i|(c_i, c_{i+1}, c_{i+2})) = 1 \tag{5}$$

This conditional probability can be interpreted as the degree of predictability of an extension of a known structure. To extend this predictability to the conditional entropy as a measure of uncertainty of extension, the term entropy is introduced now within the context of symbolic sequences.

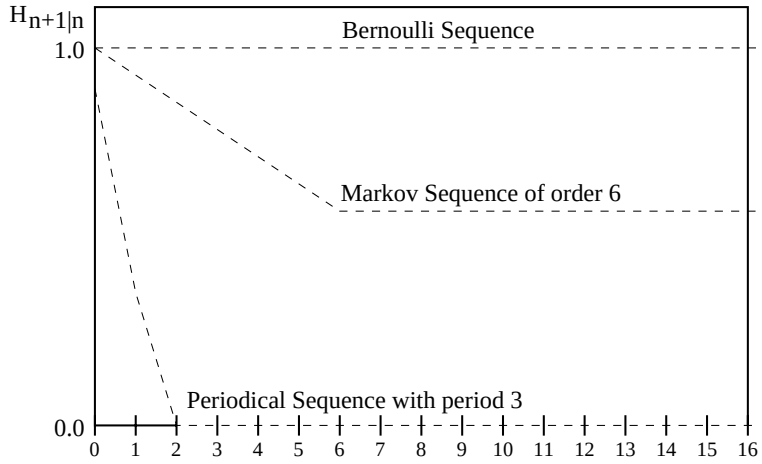


**Figure 5.** The conditional entropy depends on the range of correlations. A Bernoulli sequence shows no correlation between any two elements (refer to equation 4), thus the gain of information (i.e. the uncertainty) when extending the sequence by one element is maximal each time. A Markov sequence with limited range of memory (here within a distance of 6) shows a decreased information gain within its range of memory, but preserves a certain level of information gain when extending the sequence behind the range of its memory. The periodical sequence does not gain any information when its period is known. (after[8])

### Entropy as a Measure of Information

Based on a set of structures of different sizes, for example sequences of symbolic elements, a probability density can be defined. Furthermore, a measure of information of these substructures can be defined based on this probability density. In fact, the *block entropy*, which can be interpreted as *mean uncertainty* for a set of sequences (strings) $c \in A^n$ of length $n$ of an alphabet $A$ with $\lambda$ elements is defined as an functional $H$ of $p$[8]:

$$H_n = -\sum_{c_1,...,c_n \in A^n} p(c_1,...,c_n) \log_\lambda p(c_1,...,c_n) \tag{6}$$

To extend this approach to the problem of measuring the information gain when extending a given sequence of length n by one element, we use the definition of conditional entropy[8]:

$$H_{n+1|n} = \sum_{c_1,...,c_n \in A^n} p(c_1,...,c_n) \times -\sum_{c_n \in A} p(c_{n+1}|c_1,...,c_n) \log_\lambda p(c_{n+1}|c_1,...,c_n) \tag{7}$$

The gain of information obtained by the extension of a sequence by one element calculated by equation 7 can be used to determine the existence of relationships between subparts of a structure, since the range of correlations determine the characteristic type of information gain over several steps (see figure 5).

## 3. RESULTS

To investigate the ability to discriminate between the two groups of osteoporotic and non-osteoporotic vertebrae, the local dimension itself as well as the conditional entropy were investigated.

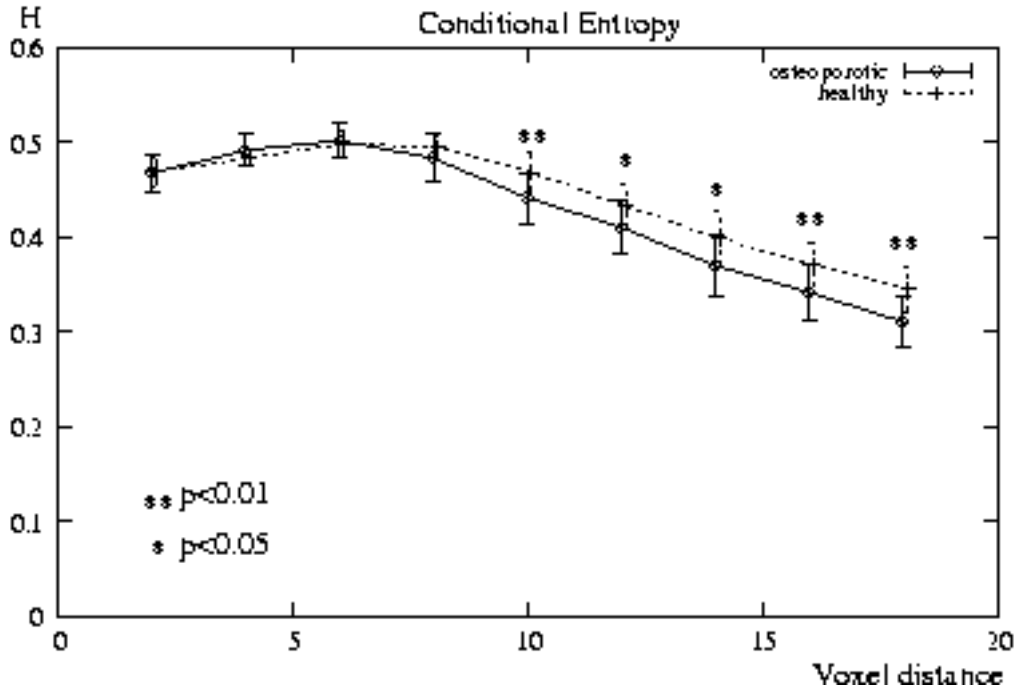


**Figure 6.** The differences of the conditional entropy increase over the distance from a starting voxel with assigned local dimension of 3. Starting from distance of 10 the differences are significant.

### Discrimination by local dimension

The local dimension which was calculated to establish a symbolic coding of the voxel space showed itself discriminative power with regard to the two groups of trabecular networks: The number of voxels of a biopsy which were assigned to a local dimension of 2 discriminated significantly ($p < 0.001$, $r^2 = 21.6\%$).

The number of voxels of assigned local dimension of 3 showed a trend ($p < 0.08$), while the number of voxels with dimension of 1 were not significant with regard to a discrimination.

### Discrimination by local entropy

All sub-trees with depths between 2 and 18 of the tree of transition probabilities were determined. Each node of a sub-tree with depth $n$ defines a sequence of transition probabilities towards this node with corresponding length $n$ which was used to calculate the conditional entropy by equation (7). Thus, each node at depth $n$ of the tree of transition probabilities corresponds to a sequence of symbols or trajectory $(c_1, \ldots, c_n) \in A^n$, and is identified as *symbolic sequence of length n* below.

For a trajectory length of 10 voxels and above, the estimation of the conditional entropy based on the transition probabilities of the symbolic coded voxel interactions showed significantly higher values for the non-osteoporotic subjects than for the osteoporotic ones (see figure 6).

In table 1 the degree of explanation of the variation between the osteoporotic and the non-osteoporotic group is given. An increase of explanatory power was found starting from sequences of length 12 and above.

| Length of symbolic sequence | $r^2$ Group discrimination (anova) |
|---|---|
| 2 | n.s. |
| 4 | n.s. |
| 6 | n.s. |
| 8 | n.s. |
| 10 | 0.25 |
| 12 | 0.16 |
| 14 | 0.19 |
| 16 | 0.23 |
| 18 | 0.30 |

Table 1: Beginning with a symbolic length of 12 an increase of the values of $r^2$ was found.

Although the two groups of vertebra did not differ significantly in terms of bone mineral density, a relationship between the conditional entropy and the BMD was investigated. Depending on the length of the sequences a weak or moderate correlation was found (see table 2). Correlations were calculated using a linear fit as well as a polynomial fit with a degree of 2.

| Length of symbolic sequence | $r^2$ (linear fit) | $r^2$ (polynomial fit (degree=2)) |
|---|---|---|
| 2 | n.s. | n.s. |
| 4 | n.s. | 0.33 |
| 6 | 0.22 | 0.24 |
| 8 | 0.23 | 0.23 |
| 10 | 0.31 | 0.31 |
| 12 | 0.4 | 0.42 |
| 14 | 0.34 | 0.36 |
| 16 | 0.34 | 0.35 |
| 18 | 0.24 | 0.24 |

Table 2: The correlation coefficients between the conditional entropy and the BMD are given for a linear correlation as well as for a polynomial fit of degree 2 (n.s. = not significant).

## 4. DISCUSSION

In the past years many approaches were investigated to describe characteristics of cancellous bone. Frequently used approaches describe directly the appearance of the trabeculae in terms of trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and trabecular number (Tb.N).[9] Other methods define more comprehensive measures like the degree of anisotropy based on the Mean Intercept Length (MIL) parameter[2] but, like the direct measures Tb.Th, Tb.N and Tb.Sp, these do not deal with the complexity of the trabecular network.

Calculations of the Fractal Dimension were applied to radiographs of cubic specimen of human trabecular bone[10] and investigated in the context of 3D-trabecular networks to discriminate between osteoporotic and healthy distal radii.[11] Additional investigations with regard to the complexity of branching trabeculae[12] were done. The application of fractal dimension assumes the existence of self similarity across several levels of magnification in the trabecular network, since this is the underlying mechanism of determining fractal dimension.

Trabecular networks represent multiple interactions of primitives of osseous connections and thus form a complex structure. Thus, concepts as the entropy, which are related to complexity may be suited to asses complex characteristics. Several measures of order, disorder and orderliness have already been defined based on a symbolic representation of 2D-HRCT images.[13] In that work, the symbolic alphabet was based on a multilevel thresholding resulting in static elements combined with measures of dynamics in terms of local gray value differences. It was found, that the complexity of a trabecular network decreases when considering the sequence of a healthy, an osteopenic and an osteoporotic network. However, while the order declines between healthy and osteopenic networks, it increases again between osteopenic and osteoporotic cases. Additionally, the definitions of the symbolic elements are closely related to the gray value levels, which may lead to the close relationships of these parameters to bone mineral density as found in that work.

In this paper, the difference of the order between the osteoporotic and non-osteoporotic group was investigated. The groups did non differ significantly with regard to BMD and age. As a result, the conditional entropy as a measure of order allowed to discriminate the two groups independently of the BMD.

To achieve the aim of comprehensively characterising complexity, our approach was based on a gray-level independent model of the trabecular network, which is not bound to a restricted set of symbols. Instead, the symbolic representation contained all possible and non ambiguous relationships in three dimensions between bone voxels with an assigned local dimension. The alphabet $A$ of 18 symbolic codes was used as the basis for constructing one dimensional structures, specifically sequences of increasing length representing voxel relationships when traversing through the voxel space. The extension of a given sequence by one symbolic coded neighbour relationship taken from the alphabet $A$ led to the calculation of the conditional entropy. This computation was enabled by a recursively calculated probabilistic tree storing the sequences of different lengths starting from a voxel with assigned local dimension of 3.

A concept of a local measure of dimension already used in the investigation of trabecular networks is the Structure Model Index (SMI).[14] Since this is a continuous measure describing plate- versus rod-like trabeculae, it would have to be mapped to symbolic values to enable its use for the evaluation of conditional entropy. Furthermore, the SMI is an integrative measure over a volume. A measure of local dimension which is applicable to each voxel of the volume appeared to be more appropriate for coding the volume with a symbolic alphabet, which forced us to use a local principal component analysis for each voxel.

When characterising natural complex structures, it may be not sufficient to restrict the research to complexity measures. A more comprehensive way has to take the stochastical character of trabecular networks into account. This lead to methods embedded in the Markov Theory. A method, which combines the requirements of modelling complexity and stochastics is the conditional entropy which was investigated in this study. There are several motivating examples of using conditional entropy in the analysis of natural and artificial sequences[8]: Natural sequences like DNA-molecules can be evaluated with this technique as well as artificial sequences like music and texts from books. For example, it was found, that music in general has lower conditional entropy and thus a higher degree of order than texts.[8]

To apply the conditional entropy to the representations of the trabecular networks obtained by Micro-CT, the continuous space voxels are embedded in had to be transfered into a discrete valued symbolic space. This transformation was performed by determination of the local dimension and the relationships between voxels. Ambiguities induced by the cylindrical form of the bone biopsies were eliminated by reducing the relationships to the distinguishable cases of horizontal and vertical relationships, resulting in an alphabet $A$ of 18 symbolic codes of voxels transitions.

The number of voxels of the local dimension calculated to determine the conditional entropy were itself significantly discriminating the two groups of osteoporotic and healthy trabecular structures: The number of voxels classified as 2-dimensional were significantly lower for the osteoporotic trabecular networks than for the healthy ones. The same was valid for the voxels of dimension of 3, although this difference showed only a trend. The voxels of assigned dimension of 1 did not show any significance. This may contribute to the thesis, that two dimensional (plate like) and three dimensional (junction like) trabeculae are lost within the progress of osteoporosis.

Furthermore, the voxels of assigned local dimension of 2 were significantly positively correlated to the failure load of the neighboured vertebrae T9-T11. Since two dimensional voxels contribute mainly to plate like trabeculae, the decrease of two dimensional voxels and thus the decrease of plates in osteoporotic networks may reduce the stability.

The conditional entropy was investigated as a measure of order of the trabecular networks. This parameter gives an estimation of how an extension of a structure is predetermined based on the given structure, but it is not mandatory bound to the colloquial understanding of the term *order* as a descriptor for self-similarity or regularity. While a structure which is regular is usually depicted as *ordered*, the conditional entropy defines order as the degree of predetermination when extending a given structure. Thus, a low conditional entropy, which is equivalent to a high degree of predetermination is necessary, but not sufficient for the property of order in the sense of regularity.

Nevertheless, the properties of a trabecular network are bound to the external forces. More precisely, the configuration of the osseous connections is forced to show regular patterns since the external forces are directed vertical through the vertebra, and typically additional osseous connections perpendicular to the horizontal connections are build. Since the trabecular network shows this regularity, a decreased predetermination may be interpreted as a loss of regularity or an increase of conditional entropy respectively. In consequence, the conditional entropy seems to be related to the regularity of the trabecular network.

Investigating the conditional entropy of the two groups of bone biopsies, the conditional entropy differed significantly between the osteoporotic and healthy structures. For lengths of 10 voxels and above we found a lower conditional entropy for the osteoporotic structures than for the healthy ones. Thus, a higher degree of predetermination or order may be assigned to the osteoporotic networks. This may be explained by the loss of horizontal vertebra and a resulting higher fraction of vertical trabeculae typically found in osteoporotic bones. Summarizing, healthy networks may show a more unordered pattern of osseous connections, while osteoporotic bones rely on the vertical trabeculae left during the osteoporotic thinning process.

The correlation of the conditional entropy and hence the correlation of the order of the trabecular network to the bone mineral density was weak or moderate, depending on the length of symbolic sequences taken into account. This result differs from the outcomes in,[13] where a strong correlation between complexity and order and the BMD was found. The reason for these different outcomes may be found in the different definitions of complexity and order.

A limitation of this study is the limited quantity of bone biopsies used. A confirmation of these results with an independent set of networks has to be done. Secondly, the probabilistic tree shows an exponential increase of branches, since the number branches leaving each node is 18. Thus, the number of nodes of each generation $x$ is given by $18^x$. Further effort is needed to optimise the algorithm in order to extend the length of sequences investigated for reasonable levels of computing power.

## 5. CONCLUSION

In this paper we have derived a method for estimating the degree of order of a trabecular network. Using this method, the hypothesis was investigated, that osteoporotic trabecular networks of human vertebra show different levels of entropy than non-osteoporotic ones. Although, for computational reasons the size of structures in which dependencies were investigated was limited to 18 voxels, this hypothesis was confirmed: for distances at and above 10 voxels osteoporotic trabecular networks showed significantly higher degree of order compared to healthy ones.

To our knowledge the conditional entropy of a trabecular network, embedded into the Markov Theory of local interactions is a new measure of osteoporotic changes of cancellous bone which may allow to assess the complex and stochastic nature of this kind of networks in an adequate way.

An independent set of trabecular networks has to be used to validate the results obtained in this study. Further optimisations of the implementation are necessary to extend the range of dependencies in order to include the intrinsic dimension of trabecular networks, which may lay outside the range observed in this study.

## ACKNOWLEDGMENTS

The authors thank Reinhard Barkmann for fruitful discussions and Felix Eckstein and Eva Maria Lochmüller for the contribution of the vertebrae.

## REFERENCES

1. T. M. Keaveny and O. C. Yeh, "Architecture and trabecular bone - toward an improved understanding of the biomechanical effects of age, sex and osteoporosis," *J Musculoskel Neuron Interact* **2**(3), pp. 205–208, 2002.

2. B. R. McCreadie, R. W. Goulet, L. A. Feldkamp, and S. Goldstein, "Hierarchical structure of bone and micro-computed tomography," in *Noninvasive Assessment of Trabecular Bone Architecture and The Competence of Bone*, S. Majumdar and B. K. Bay, eds., pp. 67–83, Kluwer Academic / Plenum Publishers, (New York), 2001.
3. R. Cowell, A. Dawid, S. Lauritzen, and D. Spiegelhalter, *Probabilistic Networks and Expert Systems*, Springer Verlag New York, Inc., 1999.
4. M. Berthold and D. J. Hand, eds., *Intelligent Data Analysis*, Springer Verlag New York, Inc., second edition ed., 1999.
5. R. Badii, *Complexity - Hierarchical structures and scaling in physics*, Cambridge University Press, 1997.
6. J. Bruske and G. Sommer, "Topology representing networks for intrinsic dimensionality estimation," in *ICANN*, pp. 595–600, 1997.
7. K. Fukunaga and D. R. Olsen, "An algorithm for finding intrinsic dimensionality of data," *IEEE Transactions on Computers* **20**(2), pp. 176–183, 1971.
8. W. Ebeling, J. Freund, and F. Schweitzer, *Komplexe Strukturen: Entropie und Information*, B. G. Teubner, Stuttgart, Leipzig, 1998.
9. A. M. Parfitt, "Bone histomorphometry: standardization of nomenclature, symbols and units (summary of proposed system)," *Bone* **9**(1), pp. 67–69, 1988.
10. S. Majumdar, J. Lin, T. Link, J. Millard, P. Augat, X. Ouyang, D. Newitt, R. Gould, M. Kothari, and H. Genant, "Fractal analysis of radiographs: assessment of trabecular bone structure and prediction of elastic modulus and strength," *Med Phys* **26**, pp. 1330–1340, Jul 1999.
11. S. Majumdar, T. M. Link, J. Millard, J. C. Lin, P. Augat, D. Newitt, N. Lane, and H. K. Genant, "In vivo assessment of trabecular bone structure using fractal analysis of distal radius radiographs," *Med Phys* **27**, pp. 2594–2599, Nov 2000.
12. D. Chappard, E. Legrand, B. Haettich, G. Chales, B. Auvinet, J. P. Eschard, J. P. Hamelin, M. F. Basle, and M. Audran, "Fractal dimension of trabecular bone: comparison of three histomorphometric computed techniques for measuring the architectural two-dimensional complexity," *J Pathol* **195**, pp. 515–521, Nov 2001.
13. P. Saparin, W. Gowin, K. J., and D. Felsenberg, "Quantification of cancellous bone structure using symbolic dynamics and measures of complexity," *Phys. Rev. E* (58), pp. 6449–6459, 1998.
14. T. Hildebrand and P. Ruegsegger, "Quantification of bone microarchitecture with the structure model index," *Comput Methods Biomech Biomed Engin.* **1**(1), pp. 15–23, 1997.