



## Analysis of genomic sequences by Chaos Game Representation

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### ABSTRACT

**Motivation:** Chaos Game Representation (CGR) is an iterative mapping technique that processes sequences of units, such as nucleotides in a DNA sequence or amino acids in a protein, in order to find the coordinates for their position in a continuous space. This distribution of positions has two properties: it is unique, and the source sequence can be recovered from the coordinates such that distance between positions measures similarity between the corresponding sequences. The possibility of using the latter property to identify succession schemes have been entirely overlooked in previous studies which raises the possibility that CGR may be upgraded from a mere representation technique to a sequence modeling tool.

**Results:** The distribution of positions in the CGR plane were shown to be a generalization of Markov chain probability tables that accommodates non-integer orders. Therefore, Markov models are particular cases of CGR models rather than the reverse, as currently accepted. In addition, the CGR generalization has both practical (computational efficiency) and fundamental (scale independence) advantages. These results are illustrated by using *Escherichia coli* K-12 as a test data-set, in particular, the genes *thrA*, *thrB* and *thrC* of the threonine operon.

**Availability:** A web page interface has been created where analyses of arbitrary sequences by CGR can be performed on-line (<http://www.itqb.unl.pt:1111/biomat/resources/resources.htm>). The test data-set used in this report is also included.

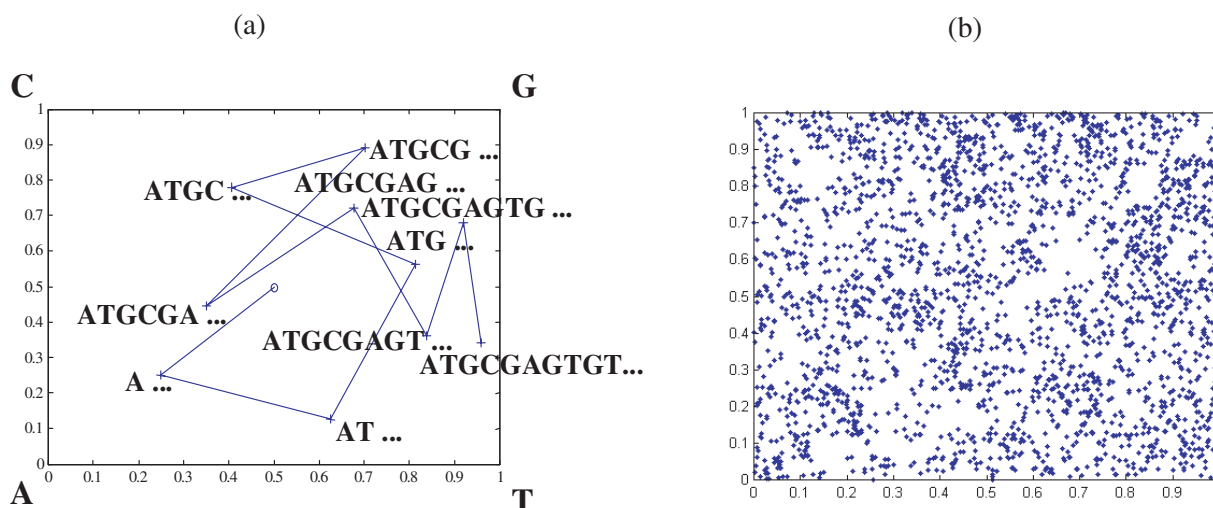
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### INTRODUCTION

Genomic sequences are in a constant state of variation due to processes such as transposition, transformation, translocation, recombination and excision (Karlin *et al.*, 1998; Casjens, 1998). Consequently, different strains of

the same species may exhibit considerable differences in global sequence due to extensive reordering of coding regions. The resulting fluidity of microbial genomes has to be taken into account when characterizing the global and local properties of sequences. Consequently, the identification of homologous regions has to follow a bottom-up approach, by first matching individual oligonucleotides, which can then be used as markers to align larger sequences (Pearson and Miller, 1992) as implemented by BLAST and FASTA (Altschul *et al.*, 1990; Altschul and Koonin, 1998; Pearson, 1996). In contrast, a top-down approach targets the statistics of nucleotide succession, which are not affected by shuffling of individual sequences. This is achieved by identifying Markov chain models (MCMs), which take the form of probability tables describing the succession scheme (Rabiner and Juang, 1986), and is further extended by hidden Markov models (HMM) for the identification of succession of alternative patterns of nucleotide succession (Krogh, 1998).

Chaos Game Representation (CGR) was proposed as a scale-independent representation for genomic sequences by Jeffrey in 1990. The technique, formally an iterative map, can be traced further back to the foundations of statistical mechanics, in particular to Chaos theory (Bar-Yam, 1997). The original proposition has been considerably expanded and generalized for sequences of arbitrary symbols (Tino, 1999), and therefore including other biological sequences such as proteins (Basu *et al.*, 1997; Pleißner *et al.*, 1997). However, the possibility that the CGR format can be used for representing the nucleotide sequence as well as identifying the resulting sequence scheme has never been fully explored. Three years after the original proposition, the translation of CGR quadrant frequencies into oligonucleotide frequencies was demonstrated and interpreted as an indication that 'it is unlikely



**Fig. 1.** (a) Chaos Game Representation (CGR) of the first 10 nucleotides of *E.coli* gene *thrA*: ATGCGAGTGT. The coordinates for each nucleotide are calculated iteratively using (0.5, 0.5) as an arbitrary starting position (equation 1). The pointer is moved half the distance to the next nucleotide to determine the next position (equation 1). (b) CGR of the full *thrA* sequence, totaling 2463 pairs of bases.

that CGRs can be more useful than simple evaluation of nucleotide, dinucleotide and trinucleotide frequencies' (Goldman, 1993). The subsequent development of HMM further relegated CGR to the status of a representation technique. The results reported below are all the more relevant as the limitations of conventional HMM for functional genomics have been increasingly noted (Baldi and Brunak, 1998). This report shows that CGR is in fact a generalized, scale-independent, Markov probability table. The CGR space is a continuous reference system where all possible sequences of any length have a unique position. Consequently, all possible nucleotide succession schemes will be encoded in the continuous space, and a new generation of scale-independent Markov models accommodating non-integer orders is made possible.

## SYSTEM AND METHODS

### Computation

The algorithms described in this manuscript were coded using MATLAB<sup>TM</sup> 5.3 language, licensed by The MathWorks Inc. (<http://www.mathworks.com>). An internet interface was also developed to make them freely accessible through user-friendly web-pages (see Availability).

### Test data

The genome of *E.coli* K-12 MG1655 was analyzed to illustrate CGR properties. The sequence was obtained from the University of Wisconsin *E.coli* Genome Project (<http://www.genetics.wisc.edu>). The test sequences corresponding to the threonine genes *thrA* (positions 337–2799), *thrB* (positions 2801–3733) and *thrC* (3734–5020)

correspond to the second, third and fourth open reading frames (ORFs), respectively.

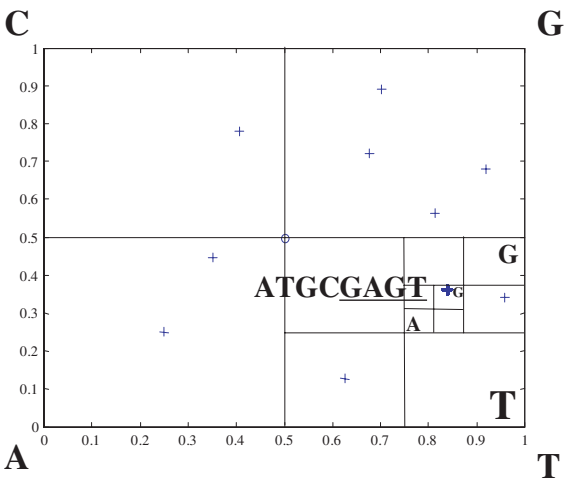
## ALGORITHM AND IMPLEMENTATION

### CGR of *E.coli* *thrA*

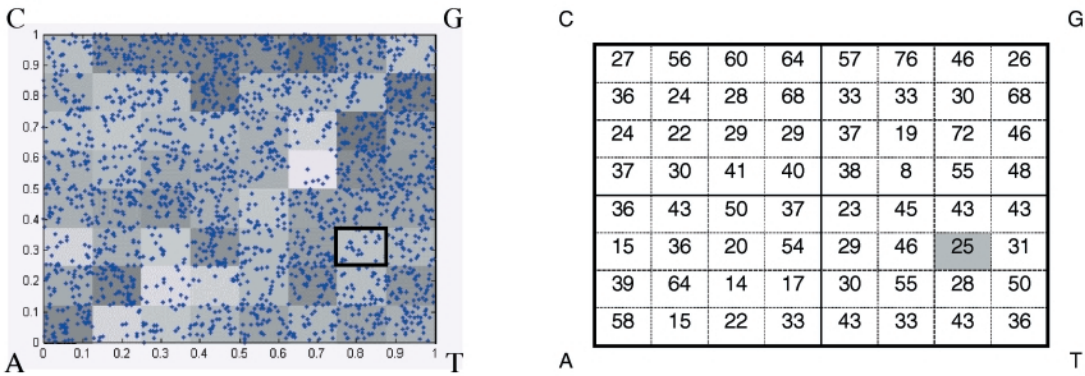
The properties of the CGR procedure (see also Jeffrey, 1990; Burma *et al.*, 1992; Deschavanne *et al.*, 1999) are hereby illustrated by analyzing the sequence of *E.coli* threonine gene *thrA*. The CGR space generated by genomic sequences is planar and is confined by the four possible nucleotides as vertices of a binary square (Figure 1). The CGR positions,  $CGR_i$ , of each nucleotide,  $g_i$ , of a sequence,  $g$  of length  $n_G$ , is calculated by moving a pointer to half the distance between the previous position and the current binary representation (equation 1). The binary CGR vertices were assigned to the four nucleotides as  $A = (0, 0)$ ;  $C = (0, 1)$ ;  $G = (1, 1)$ ;  $T = (1, 0)$ . The procedure is illustrated in Figure 1.

$$CGR_i = CGR_{i-1} + 0.5 \cdot (CGR_{i-1} - g_i) \\ \text{with } i = 1, \dots, n_G \text{ and } CGR_0 = (0.5, 0.5). \quad (1)$$

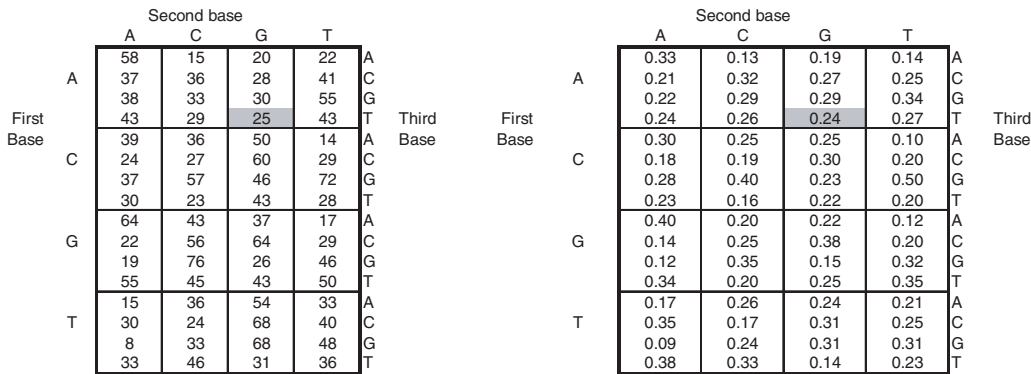
Inversely, the nucleotide sequence can also be recovered from the CGR coordinate, where the number of bases resolved is a function of the resolution of the CGR coordinates (Goldman, 1993). This is illustrated in Figure 2 for the 8th position in *E.coli*'s *thrA* gene recovered with a resolution of 4 bits for each coordinate, which implies that a sequence of 4 bases can be resolved (underlined in the figure). It is interesting to note that the position in the CGR



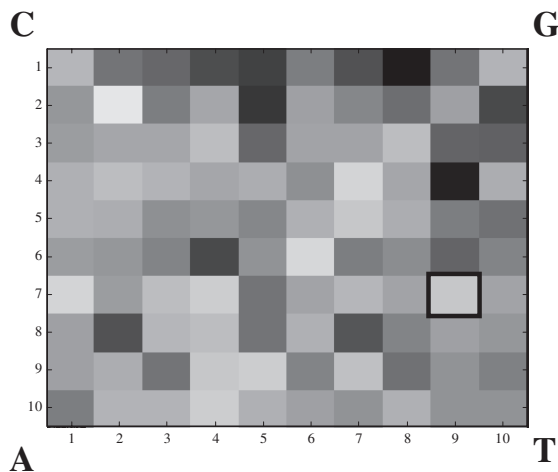
**Fig. 2.** Resolution of 8th CGR coordinate for *thrA* in order to recover the DNA sequence. If each CGR coordinate has a precision of 4 bits, the corresponding sequence will be recovered within 4 bases (underlined).



**Fig. 3.** Determination of trinucleotide frequency matrix for *thrA*. The CGR coordinates for the 2463 base pairs are plotted with the relative frequencies for each  $8 \times 8$  quadrant represented as a grayscale (left). The distribution of counts is listed in the table (right). The quadrant highlighted in the plot and in the table is defined by the vertices ...AAGT, ...CAGT, ...GAGT and ...TAGT.



**Fig. 4.** Reordering of CGR quadrant frequencies, FCGR, left, obtained for *thrA* (Figure 3), to determine the corresponding probability matrix for the second-order Markov Chain model, right, order  $n_M = n_C - 1 = 2$ . The shaded cell counts ...AGT positions (like the 8th position, Figure 1).



**Fig. 5.** FCGR<sub>ThrA,3.32</sub>: frequency  $10 \times 10$  table for CGR of *thrA*,  $k = 100 \Rightarrow n = 3.32$ . The gray scale represents frequencies between 0 (white) and the maximum frequency in any quadrant (black). The 8th position of *E.coli*'s *thrA* will now fall in the framed quadrant, delimited by ... (agga)aggaagt; ... (cgta)cgtacgt; ... (ggaa)ggaagt; ... (tgca)tgcatgt.

The conversion of FCGR to MCM is only straightforward if the number of quadrants  $k$  satisfies the condition in equation (2), necessary to produce an integer order.

$$k = 2^{n_C}, n_C \text{ is an integer } \geq 1. \quad (2)$$

However, unlike MCM, FCGR is not constrained to represent sequences with an integer number of bases. This fundamental characteristic of CGR is illustrated for *E.coli thrA* in Figure 5 where the frequency of oligonucleotides with a fractionary length has been computed by dividing the CGR plane with a  $10 \times 10$  grid ( $k = 100$  violates condition in equation (2)). The non-integer portion of a fractionary sequence quantifies a restriction or redundancy in the oligonucleotide resolution as shown below. The resolved length,  $n_C$ , can be determined by removing the condition in equation (2):

$$n_C = \log_2(k)/2. \quad (3)$$

Therefore, a  $10 \times 10 = 100$  quadrant FCGR ( $k = 100$ ) tracks the frequency of oligonucleotides with 3.32 resolved bases. The number of quadrants itself can also be non-integer (e.g. by using uneven quadrants, more below), which implies that the resolved length,  $n_C$ , can indeed be any positive real number. The identity of the fractionary sequence can be determined by calculating the delimiting sequences at the vertices of the corresponding quadrant. This is accomplished by subdividing the CGR plane consecutively as illustrated in Figure 2. For  $k = 100$ , the

8th base of *thrA* (Figure 2) would now fall in a quadrant, highlighted in Figure 5, delimited by:

$$\begin{array}{ll} \dots(\text{cgta})\text{cgta}\underline{\text{cgt}} & (\text{ggaa})\text{ggaa}\underline{\text{agt}} \\ \dots(\text{agga})\text{agga}\underline{\text{agt}} & \dots(\text{tgca})\text{tgca}\underline{\text{tgt}} \end{array}$$

The tetromers within brackets are repeated *ad infinitum* and the underlined trinucleotides correspond to the integer portion of the resolved length,  $n = 3.32$ . The definition of areas in the CGR space and the mapping of its frequency back to the sequence enables the determination of the frequency of redundant or fractionary sequences. This property of inverse frequency mapping was missed in earlier studies and the implications will be discussed below (see Discussion). By reordering the quadrants as illustrated in Figures 3 and 4 it is observed that non-integer precision in FCGR is equivalent to an incomplete higher order MCM probability table (not shown here), which is equivalent to complete MCM of non-integer order.

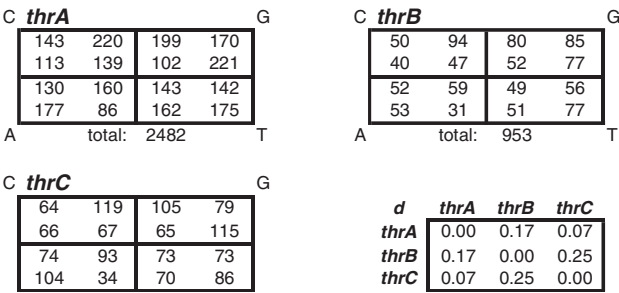
### Global distance

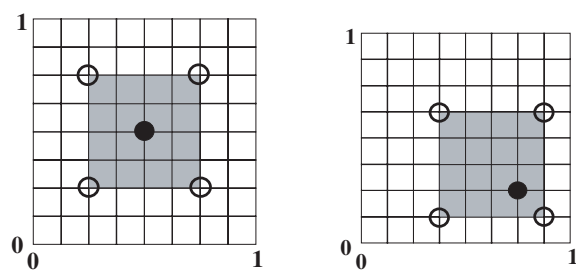
The use of FCGR to access the dissimilarity between genetic sequences can be illustrated by comparing *thrA* with the remaining two *E.coli* genes involved in the metabolism of threulose, i.e. *thrA*, *thrB* and *thrC*. These genes correspond to the second, third and fourth ORFs of *E.coli* genome and code for homoserine dehydrogenase, homoserine kinase and threonine synthase, respectively (Cami *et al.*, 1993; Malumbres *et al.*, 1995). The calculation of the global distance between sequences at any scale was based on the determination of a weighted Pearson correlation coefficient,  $r_w$  between the FCGRs (equation 4). The modification of the standard definition consisted on weighting the variance with the compounded frequency,  $nw$ , to determine the correlation between the two sets of FCGR quadrants  $x$  and  $y$ , each containing the occurrence of the same  $k$  oligomeric sequences.

$$\begin{aligned} nw &= \sum_{i=1}^k x_i \cdot y_i \\ \bar{x}w &= \frac{\sum_{i=1}^k x_i^2 \cdot y_i}{nw}, \bar{y}w = \frac{\sum_{i=1}^k y_i^2 \cdot x_i}{nw} \\ sx &= \frac{\sum_{i=1}^k (x_i - \bar{x}w)^2 \cdot x_i \cdot y_i}{nw}, \\ sy &= \frac{\sum_{i=1}^k (y_i - \bar{y}w)^2 \cdot x_i \cdot y_i}{nw} \\ rw_{x,y} &= \frac{\sum_{i=1}^k \frac{x_i - \bar{x}w}{\sqrt{sx}} \cdot \frac{y_i - \bar{y}w}{\sqrt{sy}} \cdot x_i \cdot y_i}{nw}. \end{aligned} \quad (4)$$

The advantage of using the weighted correlation coefficient defined above over using the standard definition, is





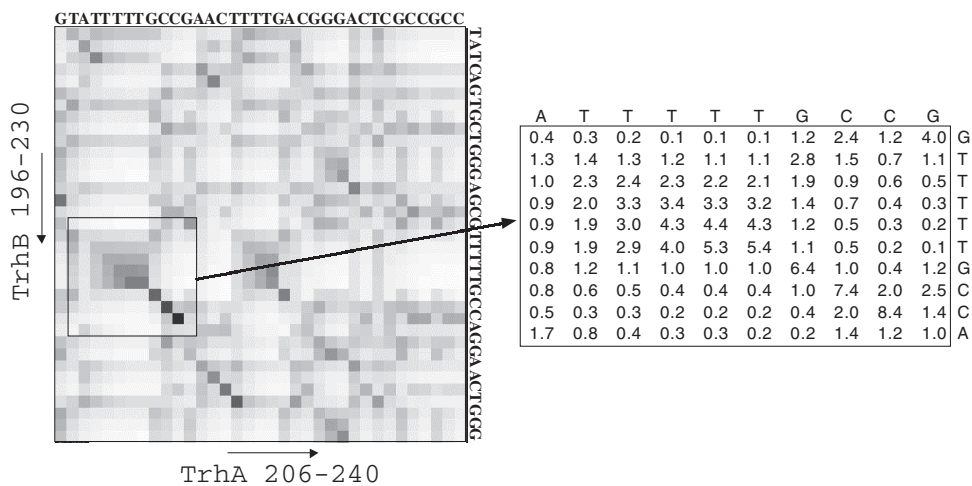


**Fig. 9.** Example of two sequences (filled circles) and the four possible positions for the sequence that ends in the next nucleotide (hollow circles). In both cases, the four possibilities are away from each other 0.5 in horizontal and/or vertical directions.

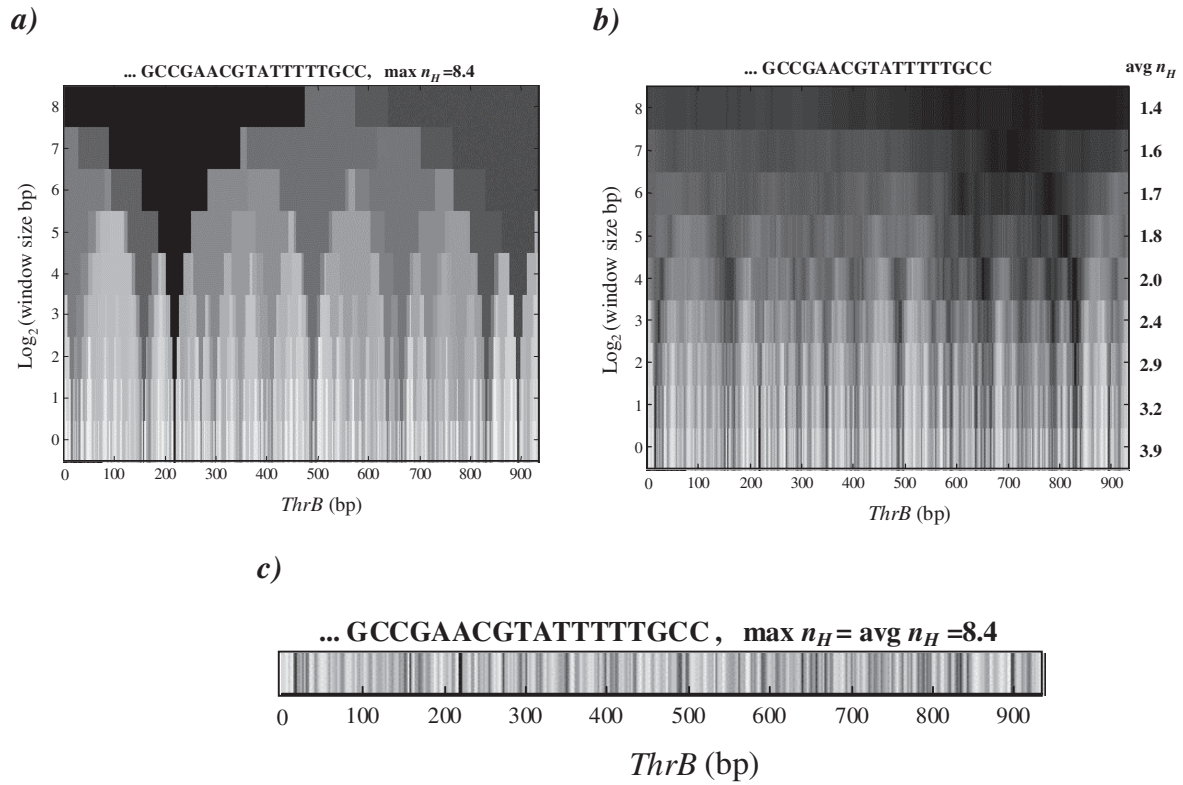
(Figure 9). Accordingly, two sequences that have the same last two nucleotides will not be further than 0.25 from each other, and a sequence of three similar last units will be no more than 0.125 apart. The existence of similar nucleotides in other positions upstream will shorten that distance (if all nucleotides are similar, the sequences being compared are equal and the distances between CGR positions will be null). This observation can be generalized in order to measure similarity as length of the similar sequence,  $n_H$ , as a function of the maximum absolute difference between either CGR coordinate (equation 6).

$$n_H = -\log_2(\max |\Delta CGR_{1...n_G}|). \tag{6}$$

The properties of  $n_H$  as a measure of similarity are illustrated in Figure 10.



**Fig. 10.** Map of similarity between two sequences of *thrA* and *thrB* genes of *E.coli* as measured by  $n_H$  (equation 6). The grayscale map on the left ranges between 0 (white) and 8.4 (black), the maximum length observed for  $n_H$  between the two sequences. The numerical values for the cross-tabulation of  $n_H$  for the longest homologous sequence (framed region zooming in a similarity of eight consecutive nucleotides) are listed on the right. The maximum value of  $n_H$  corresponds to positions *thrA* 216 and *thrB* 220.



**Fig. 11.** Similar lengths,  $n_H$ , of different positions in *thrB* to position 216 of *trhA*, determined at different scales. The grayscale is always normalized to the maximum value, in the plot title. The scale is controlled by the width of a sliding window, represented in the y-axis as the logarithm of the number of nucleotides in either direction included under the window, in addition to the nucleotide in the position being analyzed. For example, for  $\log_2(\text{window}) = 3$ , the width of the sliding window is  $1 + 2 \cdot 2^3 = 17$ . The  $n_H$  values for each position of *thrB* are represented in (c). The plot in (a) presents the maximum similar lengths in any position in the sliding window, determined for different window width lengths. The same procedure was followed to obtain (b) except that the average value was used instead.

CGR also offers new possibilities to resolve scale dependencies for information content in sequences. The convenience of using CGR for entropic studies of genomic sequences has been noted before (Román-Roldán *et al.*, 1994; Oliver *et al.*, 1993) albeit only for integer length resolutions. In order to use units consistent with the previous representations, the Shannon information number (Khinchin, 1957) was defined in sequence length units (equation 7). Each nucleotide corresponds to a maximum 2 bit information content and, therefore, logarithm base  $2^2 = 4$  was used instead of the conventional logarithm base 2. The values for  $S_4$  reported below can be compared with the literature values, reported in *bits*, by multiplying them by 2.

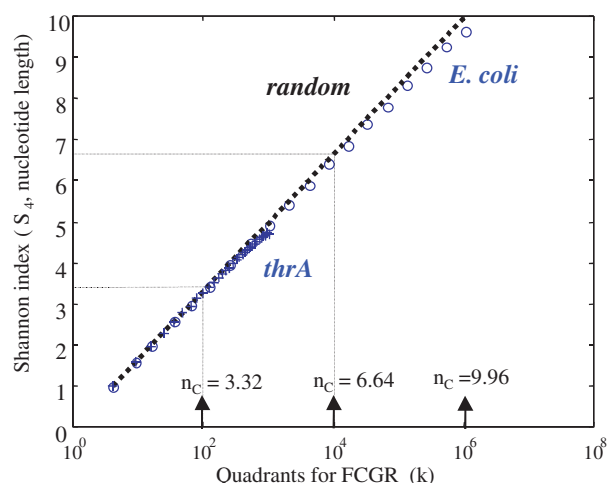
$$S_4 = \sum_{i=1}^k p_i \cdot \log_4 p_i$$

$$p_i = \frac{f(\text{quadrant}_i)}{\sum_{i=1}^k f(\text{quadrant}_i)}. \quad (7)$$

The maximum possible value of  $S_4$  would be obtained for a uniform random nucleotide sequence and is equal to the length of the oligonucleotide whose signature is being considered (e.g. for trinucleotide signatures  $\max S_4 = 3$ ). It has been noted by different authors that natural sequences can be so compacted that their statistical properties are indistinguishable from random sequences (Oliver *et al.*, 1993; Hairiri *et al.*, 1990). This perplexing characteristic can now be verified with FCGR resolved in a continuous scale. In the example below (Figure 12), the value of  $S_4$  for the entire *E.coli* genome and for the open reading frame of *thrA* are plotted together for fractional increases in the resolved length ( $n_C$ ).

## DISCUSSION

The relevance of accessing the frequency of non-integer genomic sequences may not be apparent at first given that all sequences are physically made of integer number of nucleotides. However, the loss of resolution by redundant reading is in fact equivalent to the sequence resolved



**Fig. 12.** Entropic content,  $S_4$ , of *E.coli* genome (circles), and that of *thrA* ORF (crosses). A random sequence would have an entropic content equal to the resolved length,  $n$  (dashed line). Recall that  $n_C$  is related to  $k$  by equation (3).

as being composed of a non-integer number of units (Figure 5). For example, if for a particular position A and G can be always interchanged, as can C and T, then the equivalent sequence would only encode information equivalent to 1/2 unit (using equation (3):  $k = 2, n_C = \log_2^{(2)}/2 = 1/2$ ). This is particularly relevant, as redundancy is a fundamental attribute of genome structures (Jeffrey, 1990). The degenerated translation of trinucleotides (Hsiung, 1997) is illustrative: 61 sense trinucleotide codons encode for 20 amino acids, and the remaining three nonsense codons signal for the end of transcription. The resolved length,  $n_C$ , is only 2.2 (equation 5). Synonym sense codons differ in the third nucleotide (the nonsense codons may also differ in the second position), which sets the scale for this particular redundancy. The amino acid sequence itself is also redundant in the sense that protein function is not affected by some amino acid substitutions. Redundancy in proteins is a function of position and a consequence of similar physicochemical properties between some amino acids. In conclusion, the property that is the object of natural selection, i.e. function, depends on a redundant sequence, that is to say a sequence resolved with a non-integer resolution. Consequently, functional correlations are bound to be maximal for non-integer resolutions ( $n_C$ ), which identify the relevant scale dependency.

The fact that CGR simultaneously represents sequences at different scales also allows for new measures of homology between sequences to be developed. The scale independence of CGR of genetic sequences can be used to investigate local and global homology.

## CONCLUSIONS

The CGR of sequences is a method to ordinate the entire domain of possibilities in a continuous two-dimensional space. This enables determination of global distance (equation 3) and local similarity (equation 4) for a continuous range of resolved lengths, as illustrated in Figures 6–11 using *E.coli*'s threonine operon. Consequently, the CGR transformation makes DNA sequences amenable to an entire new set of statistical analysis tools. For example, the average sequence can now be calculated by recovering the sequence of the position with the average CGR coordinates. Similarly, the standard deviation can now be determined and then converted to similar sequence length units using equation (6). For example, the *thrA* gene analyzed above has an average sequence of ATGGGGTTTCGCATCTGCTAGCACGAGAAGAGACACTGTCCGACGCGGAAAAG, the median sequence of TGGTATGCTTGACGGGGAAAAG, which has a similar length,  $n_H$ , to the average sequence of 7.7 nucleotides, which highlights a sequence distribution skewness of 0.13 unit length. Finally, the standard deviation and standard errors of *thrA* (2463 bp) sequence have similar lengths,  $n_H$ , of 4.8 and 1.8 nucleotides, respectively. This simple example illustrates the fact that CGR is a formalism that bridges between sequences of discrete units and numeric coordinates in a continuous space. Consequently, basic statistic measures and techniques can now be applied to sequences and a wide range of new tools can now be devised for statistical analysis. The utilization of multivariate statistical methods, such as cluster analysis and factor extraction was demonstrated in Figures 7 and 8. Non-hierarchical clustering methods such as Kohonen mapping and K-nearest means (Kohonen, 1997), as well as advanced classification methods such as neural networks (Bishop, 1995), can be easily applied to the FCGR of biological sequences. The authors also expect the properties of CGR to be relevant for computational and fundamental advances in the Bayesian modeling in general. The current limitations of Hidden Markov Chains to cope with simultaneous dependencies at multiple scales may be overcome by identifying multiple alternative states with CGR. This may be particularly effective when coupled with the machine learning approaches increasingly advocated (Baldi and Brunak, 1998) to extend the capabilities of Markov models.

## ACKNOWLEDGEMENTS

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