# An Unusual 500,000 Bases Long Oscillation of Guanine and Cytosine Content in Human Chromosome 21 

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#### Abstract

An oscillation with a period of around 500 kb in guanine and cytosine content ( $\mathrm{GC} \%$ ) is observed in the DNA sequence of human chromosome 21. This oscillation is localized in the rightmost one-eighth region of the chromosome, from 43.5 Mb to 46.5 Mb . Five cycles of oscillation are observed in this region with six GC-rich peaks and five GC-poor valleys. The GC-poor valleys comprise regions with low density of CpG islands and, alternating between the two DNA strands, low gene density regions. Consequently, the long-range oscillation of GC\% result in spacing patterns of both CpG island density, and to a lesser extent, gene densities.


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## 1 Introduction

Periodicities and characteristic length scales in biological sequences have been of longstanding interest in sequence analysis. The codon structure and the corresponding length scale of three bases in protein coding sequences (Shulman et al., 1981; Fickett, 1982; Staden and McLachlan, 1982) is one of the main features being used for computational gene recognization (see, e.g., Borodovsky et al., 1986; Borodovsky and McIninch, 1993; Burge and Karlin, 1997; Tiwari et al., 1997; Guigo, 1999; Grosse et al., 2000; Li et al., 2002). by a tendency for certain base types to be at certain codon positions. A correlation at a distance of 10-11 bases was also detected Trifonov and Sussman, 1980; Baldi et al., 1996; Widom, 1996; Tomita et al., 1999). Two possible explanations have been put forward to explain this (Herzel et al., 1998). The first explanation is that this periodicity is related to DNA bending and nucleosome formation (Trifonov and Sussman, 1980). The second explanation is that it is a reflection of a periodicity in protein sequences (Zhurkin, 1981), because most sequences that exhibit 10-11 base correlations are protein coding sequences (see, however, the result in (Holste et al., 2003), where a 10-11 base correlation is detected in mostly non-coding human chromosomes $20,21,22$ sequences). Proponents of the second explanation also argue that nucleosome formation is only aided by a sequence property on 5-6 bases (Zhurkin, 1981). Periodicities in protein sequences are seen to be natural, because their presence aids the secondary structure (Shiba et al., 2002). Besides these two well known length scales in DNA sequences, 3 and 10-11 bases, other length scales, e.g., 120, 200, and 450 bases, were also proposed, based mainly on a theoretical argument on the size of an exon, the size of nucleosome unit, and the size of a typical prokaryote protein (Trifonov, 1998).

Tandem repeats of DNA segments introduce local or even global sequence periodicities depending on their distribution. If a sequence of $k$ bases tandemly repeats many times, there would be base-base correlations at separations of $k, 2 k, 3 k, \ldots$ bases, e.g., the periodicity of $k=2$ bases observed in non-coding sequences (Arques, 1987; Konopka et al., 1987). If the repeat is not perfect, such as those in many subtelometric sequences, a correlation may not appear at the exact multiples of the basic unit size (Pizzi et al., 1990). Interspersed repeats in mammalian genomes (Smit, 1999) should in principle not introduce characteristic length scales in correlation patterns because their spatial distribution is not regular (except for length scales shorter than the size of one copy of the repeat). A recent survey
of characteristic length scales in many eukaryote genome sequences by spectral analysis reveals peaks in power spectra at about 68,59 and 94 bases in C. elegans (chromosomes I, II, and III, respectively), at about 248, 167, 126 bases in $A$. thaliana chromosome 3, at about $174,88,59$ bases in chromosome 4 , at about $356,174,88,59$ bases in chromosome 5, and at about 167, 84 bases in H. sapiens chromosomes 21 and 22 (Fukushima et al., 2002). A connection between these length scales and tandem or interspersed repeats for the three human chromosomes (20, 21, and 22) has been discussed in (Holste et al., 2003).

At distances much longer than hundreds of bases, it is more difficult to observe a correlation at the level of individual bases. It is, however, easier to observe correlations between base compositions, such as the guanine and cytosine content ( $\mathrm{GC} \%$ ). The reason is as follows: instead of requiring a matching base by base at the exact spacing, correlation at the base composition level only requires $\mathrm{GC} \%$ to be similarly high (or low) at certain range of spacings. In this paper, we report an unusual long-range oscillation of $\mathrm{GC} \%$ with a periodicity of around 500 kb ( $1 \mathrm{~kb}=10^{3}$ bases) in the DNA sequence of human chromosome 21. This periodicity is longer than any periodicity in DNA sequences detected so far.

## 2 The DNA sequence of human chromosome 21 exhibits higher correlations

Sequence data were downloaded from the UCSC human genome repository (available at http://genome.ucsc.edu/), for the version of NCBI build-34 release. We evenly partition each human chromosome into $N=2^{k}$ non-overlapping windows (e.g., $k=17$ and $N=131,072$ ). GC\% of each window is calculated, forming a GC\% series: $\left\{x_{i}\right\}$ $(i=1,2, \ldots N)$. The correlation function $\Gamma(d)$ of this series is defined as the Pearson's correlation coefficient of two truncated subseries: a right-hand side truncated $\left\{x^{\prime}\right\} \equiv\left\{x_{i}\right\}$ $(i=1,2, \ldots N-d)$, and a left-hand side truncated $\left\{x^{\prime \prime}\right\} \equiv\left\{x_{i}\right\}(i=d+1, d+2, \ldots N)$ :

$$
\begin{equation*}
\Gamma_{w}(d) \equiv \frac{\operatorname{Cov}\left(x^{\prime}, x^{\prime \prime}\right)}{\sqrt{\operatorname{Var}\left(x^{\prime}\right)} \sqrt{\operatorname{Var}\left(x^{\prime \prime}\right)}} \tag{1}
\end{equation*}
$$

where the covariance is defined as $\operatorname{Cov}\left(x^{\prime}, x^{\prime \prime}\right)=\left\langle\left(x^{\prime}-\left\langle x^{\prime}\right\rangle\right)\left(x^{\prime \prime}-\left\langle x^{\prime \prime}\right\rangle\right)\right\rangle$ and the variance is defined as $\operatorname{Var}(x)=\left\langle(x-\langle x\rangle)^{2}\right\rangle(\langle \rangle$ is the average of the $\{x\}$ series $)$. Here, the parameter $w$ is used to indicate the fact that the $\mathrm{GC} \%$ series, and thus detected patterns of correlation, implicitly depends on the window size $w$. When the spacing $d \ll N$, the following
approximation formula can be used:

$$
\begin{equation*}
\operatorname{Var}\left(x^{\prime}\right) \approx \operatorname{Var}\left(x^{\prime \prime}\right) \approx \operatorname{Var}(x), \quad \Gamma_{w}(d) \approx \frac{\operatorname{Cov}\left(x^{\prime}, x^{\prime \prime}\right)}{\operatorname{Var}(x)} \tag{2}
\end{equation*}
$$

For each human chromosome, Fig. 1 shows $\Gamma(d)$ for both the GC\% series derived from $2^{17}$ windows (bottom) and the GC\% series derived from $2^{15}$ windows (top). Fig. 1 shows that the magnitude of $\Gamma(d)$ depends on the window size.

We illustrate how the magnitude of the correlation function depends on the window size by plotting in Fig. 2 the correlation $\Gamma_{w}(d)$ at distance close to $d \approx 1 \mathrm{Mb}(1 \mathrm{Mb}=$ $10^{6}$ bases) for each human chromosome versus the chromosome-specific window size $w$. All $w$ values are within the range of $0.3-2 \mathrm{~kb}$. In a double-logarithmic representation, $\log \left(\Gamma_{w}(d=1 \mathrm{Mb})\right)$ for the majority of human chromosomes follows a linear function of $\log (w)$, and thus $\Gamma_{w}(d=1 \mathrm{Mb}) \sim w^{b}(b>0)$ approximates a power-law function.

The dependence of $\Gamma_{w}(d)$ on the window size $w$ shown in Fig. 2 was previously observed (Li and Holste, 2004). It can be explained as follows. As can be seen from Eq.(21), $\Gamma_{w}(d)$ depends on both $\operatorname{Cov}()$ and $\operatorname{Var}()$. While the denominator $\operatorname{Var}(\mathrm{GC} \%)$ is dependent on $w$ and gradually decreases with increasing window size, the nominator $\operatorname{Cov}(\mathrm{GC} \%)$ is practically independent of $w$. Experimentally, a slower-than-expected decrease of $\operatorname{Var}()$ with the window size was already observed around 1976 (Macaya et al., 1976). For random symbolic sequences, it can be shown by the binomial distribution that the variance of $\mathrm{GC} \%$ decreases with the window size $w$ according to $\operatorname{Var}(\mathrm{GC} \%) \sim 1 / w$ (Nekrutenko and Li, 2000; Clay et al., 2001). Sequence analysis shows, however, that $\operatorname{Var}(\mathrm{GC} \%) \sim 1 / w^{\beta}$ with $0<\beta<1$ (Clay et al., 2001; Li and Holste, 2004). This "resistance to reduction of variance" is directly related to the $1 / f^{\alpha}(\alpha \approx 1)$ power spectrum (Clay et al., 2001; Clay et al., 2003; Clay, 2003; Li, 2005) previously observed in DNA sequences (Li and Kaneko, 1992) by the relationship $\alpha \approx 1-\beta$.

Combining the lack of influence on $\operatorname{Cov}()$ by the window size, and the factor of $1 / w^{\beta}$ for $\operatorname{Var}(), \Gamma(d)$ is expected to increase with increasing window size as $\Gamma_{w}(d) \sim w^{\beta}$. Indeed, in Fig. $2 \log \left(\Gamma_{w}(d)\right)$ at $d=1 \mathrm{Mb}$ increases with $\log (w)$ more or less linearly. Excluding the outlying chromosomes $(15,21,22, \mathrm{X}, \mathrm{Y})$, the regression coefficient in Fig. 2 is $\beta \approx 0.52$. This value of $\beta$ is consistent with decay exponents by the spectral analysis (Li and Holste, 2004), but note that (i) it is an average among different chromosomes, whereas the parameter fitting in (Li and Holste, 2004) is carried out separately on individual chromosomes; and (ii) a particular distance $d \approx 1 \mathrm{Mb}$ is chosen.

Fig. 2 clearly shows that considering the trend $\Gamma_{w}(d) \sim w^{\beta}$ (at $d=1 \mathrm{Mb}$ ), chromosomes 15,22 , and Y have lower correlations than an average human chromosome, while chromosome 21 has higher correlations than the remaining chromosomes. The lower correlation in chromosome Y is caused by the large portion of unsequenced bases (about $50 \%$ ) and their substitution with random values ( Li and Holste, 2004). In the next section, we will examine closely the causes of the unusual high correlations in chromosome 21.

## 3 An oscillation of 500 kb in the correlation function is located at the rightmost one-eighth of the chromosome

Fig. 3 shows the correlation function $\Gamma(d)$ (for GC\% series calculated at the window size of $w=358$ bases) as the function of $d$, for the DNA sequences of human chromosome 21 . There is a striking oscillation in $\Gamma(d)$ which peaks at about $0.5,1.1,1.6$, and 2.1 Mb with an approximately constant spacing between peaks of about 500 kb . From Fig.1, it can be seen this long-range oscillation is solely present in human chromosome 21, but not in other human chromosomes. As discussed above, a sequence periodicity can be caused either by an exact repeat or by a tendency for a particular base to be located in a periodic location. In either case, to maintain base-level periodicity for such a distance of hundreds of kb or longer requires a selection pressure against insertion and deletion mutations.

To find out whether this 500 kb periodicity is localized in a particular region on chromosome 21, we segment chromosome 21 evenly into eight segments. Fig. 4 shows the correlation function $\Gamma(d)$ for each segment as a function of $d$. The first and the second segments are mostly unsequenced, and hence $\Gamma(d)$ is flat as unsequenced bases are substituted by random bases. In the next three chromosomal regions ( $11.7 \mathrm{Mb}-29.3 \mathrm{Mb}$ ), essentially no apparent correlation structure is present in $\Gamma(d)$ at $d=500 \mathrm{~kb} \sim 2.5 \mathrm{Mb}$ range. The gradual decay of $\Gamma(d)$ from 500 kb to 1.5 Mb in the sixth chromosomal segment ( 29.3 Mb 35.2 Mb ) is mainly due to an onset from an L2-isochore to an H1-isochore (Bernardi, 2001; Pavlícek et al., 2001). The correlation function of the last segment ( $41.1 \mathrm{Mb}-46.9 \mathrm{Mb}$ ) reveals the source of the 500 kb oscillation: the peak locations are exactly the same as those in Fig. 3 albeit without the decay trend. This segment corresponds largely to the GC-rich isochore of chromosome 21.

Fig. 5 shows the chromosomal region, from 43.5 Mb to 46.5 Mb , that exhibits the 500 kb oscillation. Fig.5(a) shows the GC\% calculated from the window size of $w=2,864$ bases.

Also shown in Fig.5(a) is a sinusoidal function with the period of 500 kb . The second half of the sinusodial function is shifted from the first half to better fit the oscillation in the GC\% fluctuation. It can be seen that six GC-high peaks alternate with five GC-low valleys, though the third valley is not as low as the others. The distance between two GC-high peaks (or GC-low valleys) is approximately equal to 500 kb , with the exception of the middle region that has a longer spacing between peaks. It is interesting to note that the alteration of GC-high and GC-low regions, but not the regularity of the spacing, had implicitly been detected before (e.g. Fig. 1 of Hattori et al., 2000, and Fig. 3 of Bernardi, 2001).

Because interspersed repeats tend to have higher GC\% than the rest of the sequence, we address the question of whether a regular spatial distribution of the repeat sequences is responsible for the observed 500 kb oscillation. Fig.5(b) shows a similar GC\% fluctuation for the sequence with substituted interspersed repeats. The 500 kb oscillation persists even when interspersed repeats are substituted.

## 4 Discussion

In this paper, we have observed a localized 500 kb long oscillation in GC\% of human chromosome 21. We checked whether the region of chromosome 21 with this oscillation has been the focus of investigations in previously large-scale correlation analyses of the human genome, and we found that a segmental duplication of size of 200 kb has been identified on chromosome 21 (Golfier et al., 2003). However, the region reported in (Golfier et al., 2003) was in the chromosome band 21q22.1, whereas the last one-eighth segment of the human chromosome 21 reported here was in the band 21q22.3.

The 21 q 22.3 band is both GC-rich and gene-rich, in marked contrast to the 7 Mb GCpoor isochore localized in 21q21.1-21q21.2 (Hattori et al., 2000). There are 68 known genes within the position of $43.5-46.5 \mathrm{Mb}$, or roughly one gene per 44 kb . As a comparison, there are total 268 genes for the whole chromosome 21 with length of 46.9 Mb , or one gene per 175 kb . Some of the genes are of interests to human disease gene mapping. For example, a rare autoimmune disease that affects the endocrine glands, called autoimmune polyglandular syndrome type I (APS1) or autoimmune polyendocrinopathy-candidiasisectodermal dystrophy (APECED) (Online Mendelian Inheritance in Man (McKusick, 1998) number 240300), was shown to be linked to markers in 21q22.3 (Aaltonen et al., 1994).

The linked region is further narrowed down to the autoimmune regulator (AIRE) gene (Aaltonen et al., 1997; Nagamine et al., 1997), located at the position $44.561-44.574 \mathrm{Mb}$.

Fig.5(c) shows the location of mapped known genes, using the knownGene field of the UCSC genome bioinformatics site (http://genome.ucsc.edu/goldenPath/gbdDescriptions.html). Genes on two DNA strands are plotted separately. When known genes on both strands are considered together, there is no visible gaps in their spatial distribution. However, strand-specific gene distribution seems to match the amplitudes of GC\% oscillations. We observe that the forward and the reverse strand alternately exhibits comparatively lower local gene densities in GC-poor valleys: 1 and 3 for the reverse strand ( - ), 2 and 4 for the forward strand $(+)$. Both strands show a lower local gene density in GC-poor valley region 5 .

We next investigated the spatial distribution of quantities that are directly related to GC\%. Fig.5(d) shows "long homogeneous genome regions" (Oliver et al., 2001) as detected by the program IsoFinder (Oliver et al., 2004). There are two interesting immediate observations: Firstly, the third valley is not as GC-poor as predicted by the sinusoidal function, which can also be confirmed by examining Fig.5(a) and (b). Secondly, there is a lack of periodic alternation between the GC-rich and GC-poor segments with comparable sizes. This can be explained by the difference in the segment or isochore view of global GC\% variation. Isochores corresponds to $\mathrm{GC} \%$ fluctuation that can be approximated by step functions. Gradual changes of $\mathrm{GC} \%$ as captured by sinusoidal functions are approximated poorly by step functions.

Fig.5(d) also shows the location of CpG islands (map extracted from the UCSC genome bioinformatics site). A visual inspection shows that CpG islands are rare in GC-poor valleys, in particular valleys No. $1,3,4$, and 5 . It is not a completely unexpected observation since one of the criteria for CpG island detection is its GC\%. In particular, one of the oftenly used methods for CpG island detection requires GC\% to be higher than $50 \%$ (Larsen et al., 1992). The GC-high peaks and GC-poor valleys in Fig. 5 are separated by the $\mathrm{GC} \%=50 \%$ line, and this may explain why CpG islands are less likely to be found in these GC-poor valleys.

In summary, we have detected a unique long-range oscillation in a localized region in human chromosome 21, which is absent in the remaining human chromosomes. It will be of interests to determine the key biological features either causing or resulting from this ultralong-ranging periodicity in human chromosome 21 . While it cannot be excluded that
this particular oscillation is due to chance events, one of the promising directions to pursue is its connection to chromatin structure and DNA loops, along the similar line of research on the connection between these structural units and GC\% (Saccone et al., 2002; Bernardi, 2004).

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## References

Aaltonen, J., Björses, P., Sandkuijl, L., Perheentupa, J., Peltonen, L., 1994. An autosomal locus causing autoimmune disease, autoimmune polyglandular disease type I assigned to chromosome 21. Nature Genetics, 8,83-87.

Aaltonen, J., et al. (The Finnish-German APECED consortium), 1997. An autoimmune disease, APECED, caused by mutations in novel gene featuring two PHD-type zinc-finger domains. Nature Genetics, 17,339-403.

Arques, D.G. 1987. Periodicities in introns. Nucleic Acids Research, 15, 7581-7592.
Baldi, P., Brunak, S., Chauvin, Y., Krogh, A., 1996. Naturally occurring nucleosome positioning signals in human exons and introns. Journal of Molecular Biology, 263,503510.

Bernardi, G , 2001. Misunderstandings about isochores. Part 1. Gene, 276,3-13.
Bernardi, G , 2004. Structural and Evolutionary Genomics (Elsevier).
Borodovsky, M., McIninch, J., 1993. GeneMark, parallel gene recognition for both DNA strands. Computers \& Chemistry, 17,123-133.

Borodovsky, M., Sprizhitskii, Yu., Golovanov, E., Aleksandrov, A., 1986. Statistical patterns in primary structures of functional regions in the E. coli genome. I. oligonucleotide
frequencies analysis. Molecular Biology, 20,826-833; II. Non-homogeneous Markov models. ibid, 20,833-840; III Computer recognition of coding regions. ibid, 20,1145-1150.

Burge, C., Karlin, S., 1997. Prediction of complete gene structures in human genomic DNA. Journal of Molecular Biology, 268,78-94.

Clay, O , 2001. Standard deviations and correlations of GC levels in DNA sequences. Gene, 276,33-38.

Clay, O., Carels, N., Douady, C., Macaya, G., Bernardi, G., 2001. Compositional heterogeneity within and among isochores in mammalian genomes. Gene, 276,15-24.

Clay, O., Douady, C.J., Carels, N., Hughes, S., Bucciarelli, G., Bernardi, G., 2003. Using analytical ultracentrifugation to study compositional variation in vertebrate genomes. European Biophysics Journal, 32,418-426.

Fickett, J.W., 1982. Recognition of protein coding regions in DNA sequence. Nucleic Acids Research, 10,5303-5318.

Fukushima, A., Ikemura, T., Kinouchi, M., Oshima, T., Kudo, Y., Mori, H., Kanaya, S., 2002. Periodicity in prokaryotic and eukaryotic genomes identified by power spectrum analysis. Gene, 300,203-211.

Golfier, G., Chibon, F., Aurias, A., Chen, X.N., Korenberg, J., Rossier, J., Potier, M.C., 2003. The $200-\mathrm{kb}$ segmental duplication on human chromosome 21 originates from a pericentromeric dissemination involving human chromosomes 2,18 and 13. Gene, 312,5159.

Grosse, I., Herzel, H., Buldyrev, S.V., Stanley, H.E., 2000. Species independence of mutual information in coding and noncoding DNA. Physical Review, 61, 5624-5629.

Guigo, R., 1999. DNA composition, codon usage and exon prediction. in Genetics Databases, ed. M Bishop, Academic Press.

Hattori, M., et al. , 2000. The DNA sequence of human chromosome 21. Nature, 405,311319.

Herzel, H., Weiss, O., Trifonov, E.N., 1998. Sequence periodicity in complete genomes of Archaea suggests positive supercoiling. Journal of Biomolecular Structure and Dynamics, 16,341-345.

Holste, D., Grosse, I., Beirer, S., Schieg, P., Herzel, H., 2003. Repeats and correlations in human DNA sequences. Physical Review E, 67,061913.

Konopka, A.K., Smythers, G.W., Owens, J., Maizel, J.V. Jr. 1987. Distance analysis helps to establish characteristic motifs in intron sequences. Gene Analysis Techniques, 4, 63-74.

Larsen, F., Gundersen, G., Lopez, R., Prydz, H., 1992. CpG islands as gene markers in the human genome. Genomics, 13,1095-1107.

Li, W., 2005. Large-scale fluctuation of guanine and cytosine content in genome sequences, isochores and 1/f spectra. in Progress in Bioinformatics. Nova Science, Hauppauge, NY.

Li, W., Bernaola-Galván, P., Haghighi, F., Grosse, I., 2002. Applications of recursive segmentation to the analysis of DNA sequences. Computers \& Chemistry, 26, 491-510.

Li, W., Holste, D., 2004. Universal 1/f noise, cross-overs of scaling exponents, and chromosome specific patterns of GC content in DNA sequences of the human genome. submitted to Physical Review E.

Li, W., Kaneko, K., 1992. Long-range correlation and partial $1 / f^{\alpha}$ spectrum in a noncoding DNA sequence. Europhysics Letters, 17,655-660.

Macaya, G., Thiery, J.P., Bernardi, G., 1976. An approach to the organization of eukaryotic genomes at a macromolecular level. Journal of Molecular Biology, 108,237-254.

McKusick, V.A., 1998. Mendelian Inheritance in Man. A Catalog of Human Genes and Genetic Disorders, Johns Hopkins University Press, Baltimore. 12th edition. URL, http,//www.ncbi.nlm.nih.gov/omim/.

Nagamine, K., et al. , 1997. Positional cloning of the APECED gene. Nature Genetics, 17,393-398.

Nekrutenko, A., Li, W.H. , 2000. Assessment of compositional heterogeneity within and between eukaryotic genomes. Genome Research, 10,1986-1995.

Oliver, J.L., Bernaola-Galván, P., Carpena, P., Román-Roldán, R., 2001. Isochore chromosome maps of eukaryotic genomes. Gene, 276,47-56.

Oliver, J.L., Carpena, P., Hackenberg, M., Bernaola-Galván, P., 2004. IsoFinder, computational prediction of isochores in genome sequences. Nucleic Acids Research, 32,W287W292.

Pavlíček, A., et al. , 2001. Similar integration but different stability of Alus and LINEs in the human genome. Gene, 276,39-45.

Pizzi, E., Liuni, S., Frontali, C. , 1990. Detection of latent sequence periodicities. Nucleic Acids Research, 18,3745-3752.

Saccone, S., Frederico, C., Bernardi, G. 2002. Localization of the gene-richest and the gene-poorest isochores in the interphase nucleic of mammals and birds. Gene, 300, 169178.

Shiba, K., Takahashi, Y., Noda, T., 2002. On the role of periodism in the origin of proteins. Journal of Molecular Biology, 320, 833-840.

Smit, A.F., 1999. Interspersed repeats and other mementos of transposable elements in mammalian genomes. Current Opinion in Genetics \& Development, 9, 657-663.

Staden, R., McLachlan, A.D., 1982. Codon preference and its use in identifying protein coding regions in long DNA sequences. Nucleic Acids Research, 10, 141-156.

Shulman, M.J., Steinberg, C.M., Westmoreland, N., 1981. The coding function of nucleotide sequences can be discerned by statistical analysis. Journal of Theoretical Biology, 88, 409-420.

Tiwari, S., Ramachandran, S., Bhattacharya, A., Bhattacharya, S., Ramaswamy, R. , 1997. Prediction of probable genes by Fourier analysis of genomic sequences. Computer Applications in Biosciences, 13, 263-270.

Tomita, M., Wada, M., Kawashima, Y., 1999. ApA dinucleotide periodicity in prokaryote, eukaryote, and organelle genomes. Journal of Molecular Evolution, 49,182-192.

Trifonov, E.N., Sussman, J.L., 1980. The pitch of chromatin DNA is reflected in its nucleotide sequence. Proceedings of the National Academy of Sciences, 77,3816-3820.

Trifonov, E.N., 1998. 3-10.5-200- and 400-base periodicities in genome sequences. Physica A, 249,511-516.

Widom, J., 1996. Short-range order in two eukaryotic genomes, relation to chromosome structure. Journal of Molecular Biology, 259,579-588.

Zhurkin, V.B., 1981. Periodicity in DNA primary structure is defined by secondary structure of the coded protein. Nucleic Acids Research, 9,1963-1971.








Figure 1: Correlation function $\Gamma(d)$ of the $\mathrm{GC} \%$ series with $2^{k}$ GC values ( $k=15$ : dots, top; and $k=17$ : lines, bottom), obtained from all 24 human chromosomes ( 22 autosomal and 2 sex chromosomes). The x -axis, in a logarithmic scale, is the distance $d$ converted to units of $\mathrm{Mb}\left(10^{6}\right.$ bases).


Figure 2: Correlation $\Gamma_{w}(d)$, at the distance $d \approx 1 \mathrm{Mb}$, as a function of the chromosome-specific window size $w$ (in a double logarithmic plot). Each point represents one human chromosome. The window size $w$ is the chromosome length divided by $2^{17}$.
auto-correlation function for chr21


Figure 3: Correlation function $\Gamma(d)$ of the GC\% series for the DNA sequence of human chromosome 21. $\mathrm{GC} \%$ is calculated at the window size of 358 bases, which is $1 / 2^{17}$ of the total chromosome length. The distances of $0.5,1,1.5$, and 2 Mb are marked by long vertical lines, and the spacing of 100 kb is marked by short vertical lines.


Figure 4: Correlation function $\Gamma(d)$ of the GC\% series for eight chromosomal regions of the DNA sequence of the human chromosome 21 . The distances of $0.5,1,1.5$, and 2 Mb are marked by vertical lines.


Figure 5: GC\% fluctuations of the last one-eighth segment of the DNA sequence of human chromosome 21 towards the q-term end. (a) GC\% calculated for the window size of $w=2.864 \mathrm{~kb}$, which is $1 / 2^{14}$ of the whole chromosome length. A sinusoidal function with the period of 500 kb is superimposed on the plot to fit the periodic oscillation of $\mathrm{GC} \%$. (b) $\mathrm{GC} \%$ calculated with interspersed repeats replaced by random values, then smoothed by means of running medians, using the S-PLUS subroutine smooth . (c) Locations of known genes as determined by protein sequences from SWISS-PROT, TrEMBL, and TrEMBL-NEW, and their corresponding mRNAs from GenBank, displayed separately for each DNA strand. (d) Locations of CpG islands (top) and isochores (bottom). For the isochore map, the GC\% of individual isochores is indicated by the height of the horizontal bar.


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