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Structural bioinformatics

SCHIP: statistics for chromosome interphase positioning based on interchange data

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ABSTRACT

Motivation: The position of chromosomes in the interphase nucleus is believed to be associated with a number of biological processes. Here, we present a web-based application that helps analyze the relative position of chromosomes during interphase in human cells, based on observed radiogenic chromosome aberrations. The inputs of the program are a table of yields of pairwise chromosome interchanges and a proposed chromosome geometric cluster. Each can either be uploaded or selected from provided datasets. The main outputs are *P*-values for the proposed chromosome clusters. SCHIP is designed to be used by a number of scientific communities interested in nuclear architecture, including cancer and cell biologists, radiation biologists and mathematical/computational biologists.

Availability: http://cramer.stat.ub.es/schip

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Supplementary information: http://cramer.stat.ub.es/schip/help.htm

During interphase, each chromosome is predominantly confined to its chromosome territory (for a review see Cremer and Cremer, 2001). Considerable randomness has been found in the juxtapositions of chromosome territories (Cornforth *et al*., 2002; Arsuaga *et al*., 2004). Nevertheless, deviations from a totally random picture have been found and attributed to different chromosome geometric clusters such as the nucleolus chromosomes (Parada and Mistelli, 2002), a cluster of five gene-rich chromosomes (Boyle *et al*., 2001) or a cluster of small chromosomes (Cremer and Cremer, 2001). Some of these chromosome clusters have been associated with biological phenomena such as gene content, gene expression or cancer (e.g. Parada and Mistelli, 2002).

We present a web-based application that helps analyze the relative position of chromosomes in human cells during G_0/G_1 phase of the cell cycle by assigning *P*-values to pre-selected chromosome geometric clusters. Proximity between any two chromosomes is estimated by the frequency with which they interact in radiation-induced interchanges. Significant deviations from the null hypothesis of random chromosome–chromosome spatial associations are assessed by Monte Carlo computer simulations.

The program requires two input sets: a table of yields of pairwise chromosome interchanges and a proposed cluster of chromosomes.

Table of yields of pairwise chromosome interchanges. The yield of pairwise chromosome interchanges between two chromosomes i and j [denoted by $f(i,j)$] is the number of cells that contain at least one interchange between chromosomes i and j with $i \neq j$, since intra-chromosomal aberrations and inter-chromosomal aberrations between homologous chromosomes cannot be detected. The table of yields can be either selected from one of the five different datasets provided or uploaded by the user. The provided tables have been generated by analyzing ionizing radiation induced chromosome aberrations. When radiation tracks (e.g. X-rays, alpha particles, etc.) cross a cell nucleus they introduce double-stranded breaks in the DNA. When the breaks are misrepaired, they can form interchanges, i.e. aberrations involving misrejoining of different chromosomes. It has been a long standing hypothesis that chromosomes in spatial proximity will form interchanges more readily than chromosomes that are far apart (Chen *et al*., 1996; Nikiforova *et al*., 2000; Bickmore and Teague, 2002; Cornforth *et al*., 2002; Roix *et al*., 2003; Arsuaga *et al*., 2004; for a review see Sachs *et al*., 2004).

Chromosome clusters. A chromosome cluster is a set of chromosomes whose members are believed to be closer to each other than randomness would predict. Chromosome clusters are provided or can be uploaded by the user. Some of the provided chromosome clusters have been proposed in the literature; others correspond to recurrent translocations reported in the Mitelman database (Mitelman *et al*., 2004, http://cgap.nci.nih.gov/Chromosomes/Mitelman). In this version of the software, we only considered recurrent translocations in lymphoblastic leukemia, not all cancers, because studying aberrations in solid tumors is believed to be less informative.

Computation of significance of clusters. The mathematical basis for the Monte Carlo algorithm has been discussed previously (Cornforth *et al*., 2002; Arsuaga *et al*., 2004). In brief, *P*-values associated with candidate clusters are measured according to the one-sided statistic $\sum \Delta(j,k) = \sum[f(j,k) - g(j)g(k)]/[(g(j)g(k))]^{1/2}$

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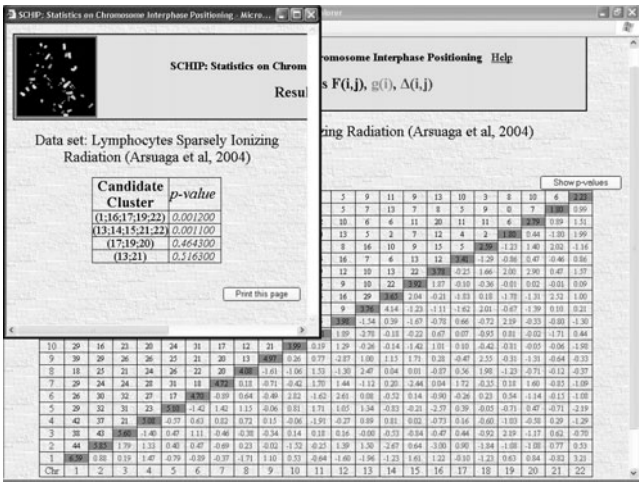

Fig. 1. Example of the output.

where $\sum$ denotes the sum over all members of the selected clusters, $f(i,j)$ is the pairwise chromosome yield and $g(i)$ is a normalized quantity that reflects single chromosome participation. This method allows one to combine data on simple and complex aberrations, aberrations observed at various doses and aberrations from different post-irradiation metaphases. This method also circumvents theoretical assumptions about aberration formation mechanisms or radiosensitivity of individual chromosomes (Cornforth *et al*., 2002; Arsuaga *et al*., 2004).

Output of the program. The first output of the program is a table that includes values of all chromosome yields ($f(i,j)$), of all auxiliary statistics $\Delta(i,j)$ and of the normalized single chromosome yield $g(i)$. These results are shown in Figure 1. Values of $f(i,j)$ are shown above the diagonal, values of $\Delta(i,j)$ are shown below the diagonal and the values of $g(i)$ are shown along the diagonal. The second output is the P-value computed for each of the selected chromosome clusters. This is a powerful new way to get an independent check for many geometric features of chromatin organization that are currently under investigation.

Future research. We are currently investigating how to incorporate results from other groups who have studied chromosome proximity using constitutional translocations and translocations found in cancer (e.g. Bickmore and Teague, 2002).

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