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► To cite this version:

Justine Rudewicz, Hayssam Soueidan, Audrey Gros, Gaetan Macgrogan, Hervé Bonnefoi, et al.. Bioinformatics methods for analyzing anti-hormonal treatment resistance in breast cancer. BCBB 2014 (Bordeaux Computational Biology and Bioinformatics), Nov 2014, Bordeaux, France. hal-01120049

HAL Id: hal-01120049

<https://hal.science/hal-01120049>

Submitted on 24 Feb 2015

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Bioinformatics methods for analyzing anti-hormonal treatment resistance in breast cancer

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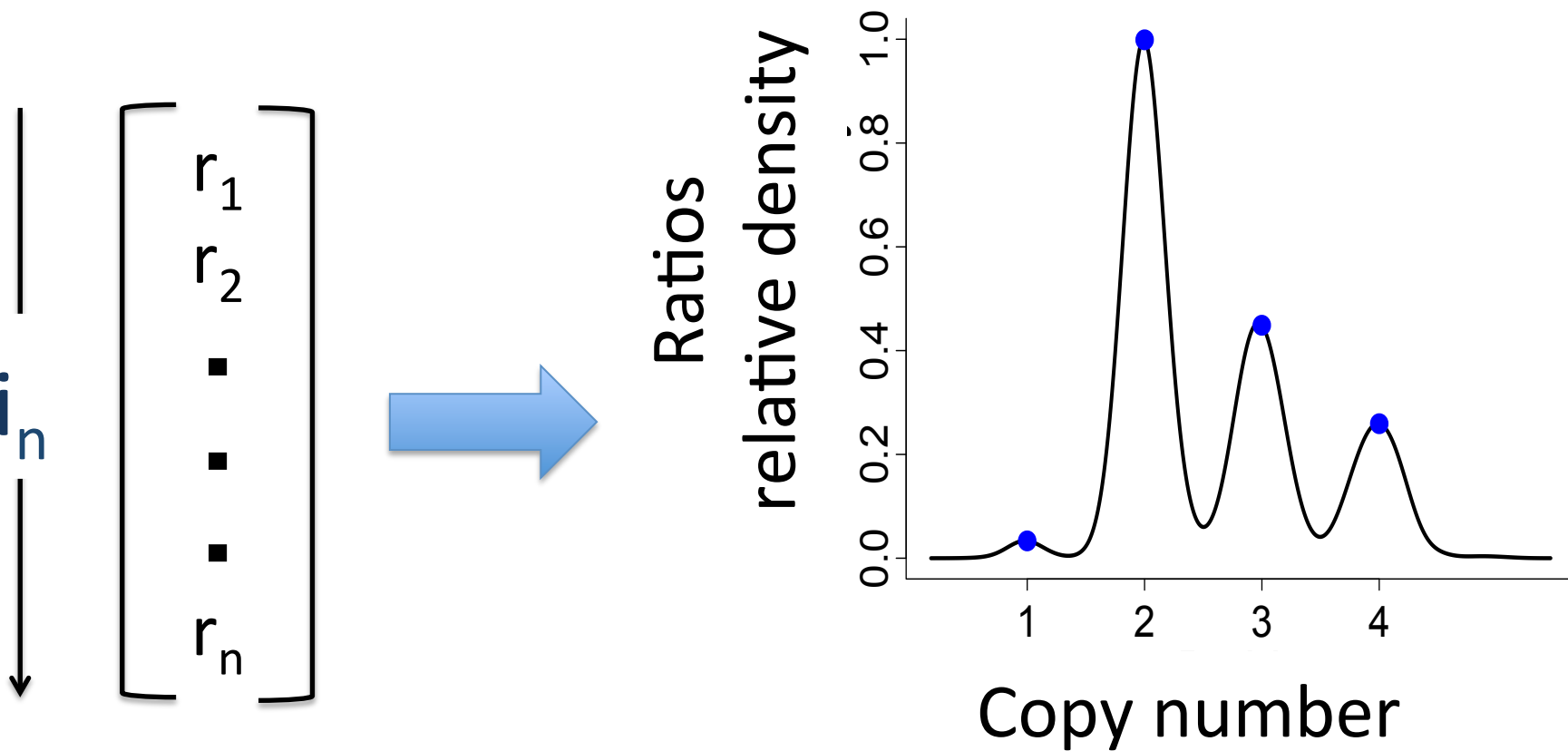
Context

One in eight women are affected by breast cancer. Most of them receive hormonal therapy. Neoadjuvant hormonal therapy is a form of hormonal therapy given before surgery. Treatment for 6 months causes tumours to shrink, after which residual tumour is removed by surgery. Unfortunately, in some cases, the tumour cells are resistant to hormonal therapy and the patients relapse. This can be caused by **intra-tumour heterogeneity**: hormonal therapy eliminates drug-sensitive clones, leaving behind resistant clones. **Understanding why some clones are resistant** and what their characteristics are may lead to the development of alternative therapies.

HORGEN copy number study

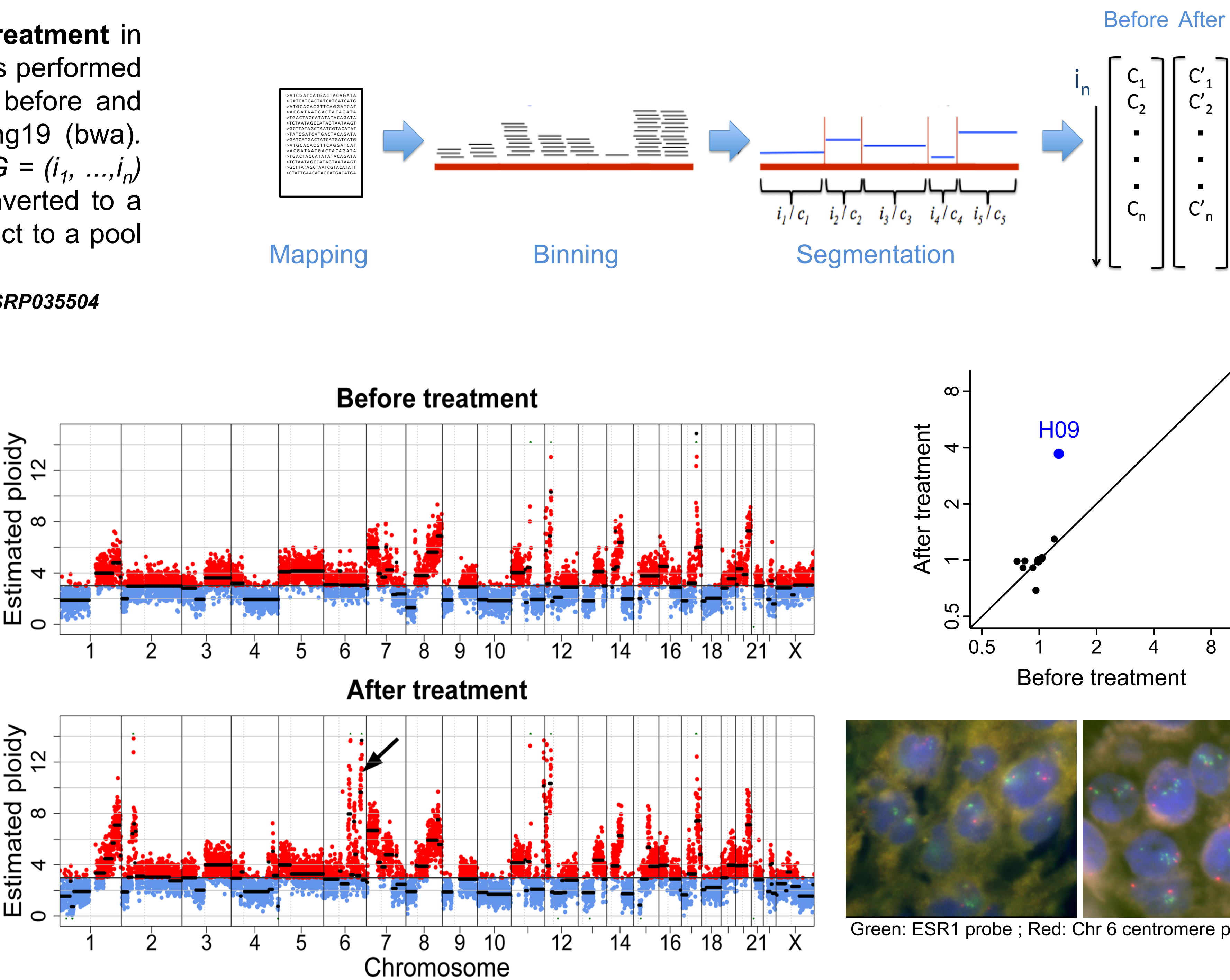
We compare DNA copy number profiles before and after treatment in the case of ER+ breast cancers. Very low depth sequencing was performed (Illumina GAIIX technology) on biopsies from breast tumours, before and after treatment. Reads were aligned to the human genome hg19 (bwa). CNAnorm was used to partition reference genome in intervals $G = (i_1, \dots, i_n)$ of non-overlapping sliding windows. Number of reads was converted to a count vector $C = (c_1, \dots, c_n)$ and then to a ratio vector with respect to a pool of normal female DNA.

Bam files available in the NCBI Sequence Read Archive under accession number SRP035504



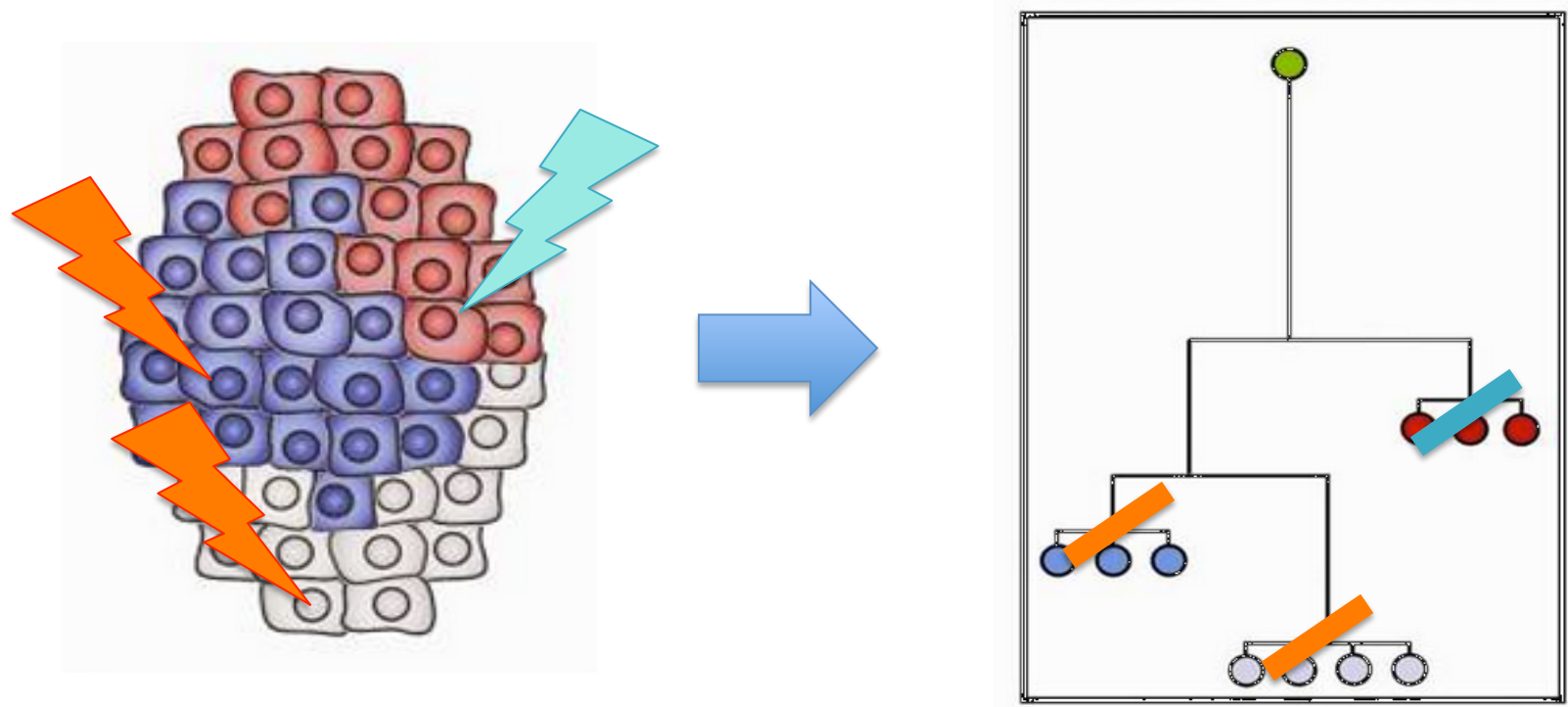
Density of ratios was used to identify different ploidy levels and to assign it to overall intervals G.

Sample H09: new amplicons appeared in the copy number profile after treatment, including an amplicon on chromosome 6q containing the ER gene (ESR1). In the same way, the normalized segmented copy number ratio of the individual ESR1 gene before and after treatment shows this amplification. FISH confirmed that the amplicon was present after treatment.



Future work

Very low depth sequencing indicates that there is a clonal selection under anti-hormonal treatment. **To confirm our finding** and better characterise clonal evolution during estrogen deprivation, we will perform **deep sequencing** of constitutive and tumour DNA before and after treatment.



Future work: We will reconstruct tumour from point mutations, copy number aberrations and their distribution in the clones. This analyses allow the identification of different cell populations present in the tumour, their proportions and genomic variations but also the phylogenetic links between them to understand mechanisms of clone resistance and characteristics of resistant clones

