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Letter to the Editor

Are Mutations in Genetically Modified Plants Dangerous?

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Latham et al. [1] and Wilson et al. [2] reviewed the long known phenomenon that plant transformation may cause mutations. Mutations can occur at any position in the genome, due to the tissue culture phase or other factors. Furthermore, insertion mutations may be induced by *Agrobacterium*-mediated transformation or particle bombardment. The authors focus in particular on mutations and chromosomal rearrangements flanking the insertion of the T-DNA. In their view, these mutations pose a risk regarding biosafety. The transgenic plant should in their opinion be as identical to its parent as possible. Therefore, they recommend extended backcrossing for elimination of genome-wide mutations, and sequencing of flanking DNA of 50 kbp at each side of the insertion, and discarding of plants that show any mutation in the flanking DNA compared to the parent plant. These and other precautions should ensure that transformation-induced mutations will not impact on biosafety.

Apparently, the authors suggest that in addition to the inserted transgene, mutations have their own contribution to uncertainties regarding biosafety. If the transgenic plant was to be released in the environment, genotypes with mutations should be discarded.

The authors do not mention mutation breeding of plants. Since the discovery of X-ray induced mutations in barley nearly 80 years ago (Stadler [3]), plant breeders and geneticists have realized how DNA mutations can be induced for widening the genetic variation in their germplasm. During the past seventy years, mutation breeding led to more than 2250 plant varieties (Maluszynski et al. [4]; Ahloowalia et al. [5]). 70% of these varieties were released as directly induced mutants, and the other 30% from crosses with induced mutants. The use of chemical treatments was relatively infrequent, but gamma rays were frequently used (64%), followed by X-rays (22%) (Ahloowalia et al. [5]).

The freely accessible FAO/IAEA website contains a database of plant varieties derived from induced mutations (http://www-infocris.iaea.org/MVD/default.htm). This list has been composed on the basis of official information from plant breeders and authorities. The composers of the database mention that the list is far from complete, as frequently it is not published how new varieties have been obtained. In spite of that, the list contains now (August 2007) already 2543 released plant varieties. In reality, the number of induced mutant varieties is much larger. If spontaneous mutants would also be included, the list would further expand strongly.

The induced mutant varieties have been developed in 175 plant species, including rice, wheat, barley, cotton, rapeseed, sunflower, grapefruit, apple, banana, and many other species. They are released in Europe, Asia, North America, South America, and Australia. Dozens of these varieties are grown at large scales (Ahloowalia et al. [5]). Many millions of people eat and use products of these varieties.

The authors also do not mention the experiences in wheat breeding with gene transfer from wild species using induced translocations. In this approach, a resistance gene was introgressed by means of an interspecific cross followed by repeated backcrosses. This led to addition of an alien chromosome, containing the resistance gene. For adoption of the resistance gene into the wheat chromosomes, the addition lines were irradiated for mutation induction. During repair of the breakages of the wheat chromosomes, sometimes a part of the alien chromosome was incorporated, leading to

normal Mendelian inheritance of the resistance gene in the wheat genome (Friebe et al. [6]; Mukai et al. [7]). Many wheat varieties have been released that contain one or more of these kinds of induced translocations.

The authors did not mention that in conventional breeding, traits from wild germplasm are introduced into cultivars by means of crosses and backcrosses with an elite cultivar. During this process, chromosomal parts from the wild germplasm are introduced. These chromosomal parts may harbour hundreds of unknown "wild" alleles and thousands of deviations in the DNA sequence compared to the original elite cultivar. These thousands of natural deviations can be regarded as thousands of mutations. We all use and eat such cultivars for many decades.

The mutant varieties and those originating from translocation events or backcrosses usually are not molecularly characterized by DNA sequencing, nor compared with their parents at the DNA sequence level. Sometimes cytogenetic or genetic marker studies are performed to locate introduced chromosomal parts in the recipient genome. However, the plant breeders of mutant varieties usually do not know the number of mutations or changes, the kinds of mutations, nor the number of rearrangements in their varieties. Neither they know whether new *open reading frames* or fused genes have been created by the mutations, nor whether expression levels of genes have changed due to mutation, or due to introgression of DNA from wild germplasm. However, the cultivars generally have been phenotyped thoroughly by the breeders and compared phenotypically to their parents and contemporary cultivars in view of their commercial value. In spite of the absence of molecular characterization, the cultivars, either from induced mutation, spontaneous mutation, or introgression breeding, have been widely accepted, grown, and used.

The precautionary measures proposed by Latham et al. [1] and Wilson et al. [2] for genetically engineered plants regarding detection of mutations are not in balance at all with common practice in conventional plant breeding as described above. It is unscientific to propose screening flanking DNA of 50 kbp at each side of the insertion, requiring discarding of plants that show any changes there, but simultaneously accepting plants with tens or hundreds or thousands of unknown but probably more dramatic DNA changes after irradiation or introgression.

One could react with a proposal to put also plants from induced mutations under strict safety regulations. This would make sense only if the mentioned 2543 varieties would have induced more frequently biosafety problems then varieties from cross breeding. However, we are not aware of any biosafety problem caused by an induced mutation of a released variety or by an induced translocation. Apparently, the common thorough evaluation of induced mutants at the phenotypic level by the breeders suffices.

Proposing a ban on mutations caused by gene transformation for the sake of biosafety indicates a blind spot for the safety of numerous mutations induced by conventional breeders for more than 70 years, and introgression of unknown chromosomal parts from wild germplasm since centuries.

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GENOMIC SIGNAL PROCESSING AND STATISTICS

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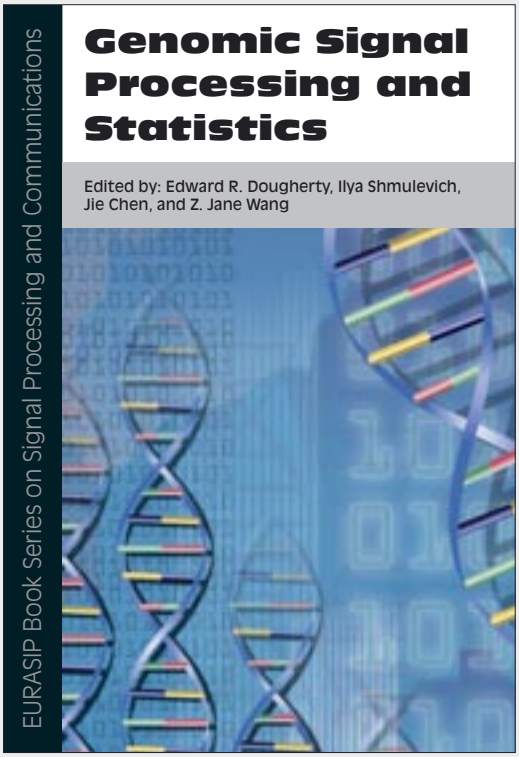

Recent advances in genomic studies have stimulated synergetic research and development in many cross-disciplinary areas. Genomic data, especially the recent large-scale microarray gene expression data, represents enormous challenges for signal processing and statistics in processing these vast data to reveal the complex biological functionality. This perspective naturally leads to a new field, genomic signal processing (GSP), which studies the processing of genomic signals by integrating the theory of signal processing and statistics. Written by an international, interdisciplinary team of authors, this invaluable edited volume is accessible to students just entering this emergent field, and to researchers, both in academia and industry, in the fields of molecular biology, engineering, statistics, and signal processing. The book provides tutorial-level overviews and addresses the specific needs of genomic signal processing students and researchers as a reference book.

The book aims to address current genomic challenges by exploiting potential synergies between genomics, signal processing, and statistics, with special emphasis on signal processing and statistical tools for structural and functional understanding of genomic data. The book is partitioned into three parts. In part I, a brief history of genomic research and a background introduction from both biological and signal processing/statistical perspectives are provided so that readers can easily follow the material presented in the rest of the book. In part II, overviews of state-of-the-art techniques are provided. We start with a chapter on sequence analysis, and follow with chapters on feature selection, clustering, and classification of microarray data. The next three chapters discuss the modeling, analysis, and simulation of biological regulatory networks, especially gene regulatory networks based on Boolean and Bayesian approaches. The next two chapters treat visualization and compression of gene data, and supercomputer implementation of genomic signal processing systems. Part II concludes with two chapters on systems biology and medical implications of genomic research. Finally, part III discusses the future trends in genomic signal processing and statistics research.

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