

Objection against Patent Application

of

Association of Swiss Cattle Breeders (Arbeitsgemeinschaft Schweizerischer Rinderzüchter, ASR), Vilettemattstrasse 9, 3000 Berne 14, Switzerland.
General Manager: Hans Künzi,

against

**MARKER ASSISTED BEST LINEAR UNBIASED PREDICTED (MA-BLUP):
SOFTWARE ADAPTIONS FOR PRACTICAL APPLICATIONS FOR LARGE
BREEDING POPULATIONS IN FARM ANIMAL SPECIES (WO2005078133)**

filed by Monsanto Technology LLC

1. The EPA should refrain from granting a patent based on WO2005078133 to Monsanto Technology LLC.
2. All costs, fees, expenses etc. should be borne by Monsanto Technology LLC.

Introduction

The following text shall demonstrate that the claims made in the above mentioned patent application are not suitable to justify the patent to be granted, primarily because all of the elements were in the public domain prior to the relevant date of priority. The claims from the patent application are given in *italics*, followed by our objection against the claim in normal font. The numbers referring to the claims are taken from the patent application. The literature cited in the text below is provided as copies of the original articles or the articles themselves. When books or manuals are cited, only the relevant chapters are provided. Texts available on the internet without any costs are not provided. This objection was prepared in collaboration with Dr. Christian Stricker, Börtjistrasse 8b, 7260 Davos, Switzerland. He will file the same objection as a private person. The association of Swiss Cattle Breeders is filing the objection as a legal entity.

Claims and Objections

1. *A method of increasing an animal population's average genetic merit, comprising; a. selecting one or more traits for which an improved genetic merit is desired; b. selecting one or more quantitative trait locus (QTL) for each selected trait; c. selecting three or more molecular genetic markers of interest for each QTL for each selected trait; d. providing databases comprising: i. genotype data for three or more molecular genetic markers for each selected trait, for a plurality of animals in the population; ii. data providing the pedigree for each animal in the population; iii. optionally, data for one or more fixed effects; e. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to calculate a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits.*

Claim 1a, i.e. “*A method of increasing an animal population's average genetic merit, comprising; a. selecting one or more traits for which an improved genetic merit is desired*” is not a novel approach at all. In fact, it is obviously pursued by virtually all breeding organisations for livestock species around the world as their main purpose. Thus, it is absolutely invalid to claim improving the average genetic merit of an animal population for a trait for which a genetic merit is desired to be a novel approach.

Claim 1b, i.e. “*A method of increasing an animal population's average genetic merit, comprising; b. selecting one or more quantitative trait locus (QTL) for each selected trait*” is not a novel approach either. Such a method has been presented Fernando and Grossman (1989). Their method was extended by Goddard (1992) and Fernando (2004) extended and clarified those approaches in the context of disequilibrium (statistical non-independence between marker and QTL) and QTL selection. Therefore, such methods have existed long before the herein mentioned patent application respectively the relevant priority date. Dekkers (2004) gives an overview of commercial applications of marker-assisted selection in livestock. His paper represents the state of the art in the year 2003, i.e. just before the above mentioned patent application was filed. Therefore, improving the average genetic merit of an animal population by selecting one or more QTL for each selected trait is not a novel approach.

Claim 1c, i.e. “*A method of increasing an animal population's average genetic merit, comprising; c. selecting three or more molecular genetic markers of interest for each QTL for each selected trait*” is not a novel approach for the same reasons given against claim 1b. In animal breeding the discovery of molecular genetic markers allowed to study genetic linkage of those markers with QTL. Markers are

polymorphic loci which are usually not expressed on the phenotypic level. However, the genetic location of markers (i.e. where they are located on the chromosome) is known and their genotyping is easy. Thus, if a relationship between markers and QTL is present, then that relationship would provide information about the position of the QTL on the chromosome. Knowing the position of a QTL allows to genotype an animal specifically for the QTL and the alleles at the QTL would provide information about the genetic value of such an individual. Even without knowledge of the exact position of a QTL on a chromosome, marker information can be used to infer information at the QTL underlying the trait of interest. This information can be used in genetic evaluation. This is exactly what the papers of Fernando and Grossman (1989), Goddard (1992) and Fernando (2004) given against claim 1b contain: A method to incorporate information from one, two, three and more molecular genetic markers into the genetic evaluation for a trait of interest. Whether to include marker or QTL information in a genetic evaluation method is methodologically and legally irrelevant since each QTL can be modeled as a marker with zero distance between marker and QTL. Therefore, the papers by Fernando and Grossman (1989), Goddard (1992) and Fernando (2004) identify claim 1b and 1c to be non-novel approaches.

Claim 1d, i.e. *“A method of increasing an animal population's average genetic merit, comprising; d. providing databases comprising: i. genotype data for three or more molecular genetic markers for each selected trait, for a plurality of animals in the population; ii. data providing the pedigree for each animal in the population; iii. optionally, data for one or more fixed effects”* is not a novel approach for obvious reasons. Databases to store pedigree and genotype data for a plurality of animals in the population have been in place for years at a large number of breeding organisations world-wide. For example, the Swiss Brown Cattle Breeders' Federation located in Zug, Switzerland, and the Red and White Cattle Breeding organisation located in Zollikofen, Switzerland store information of all available ancestors of the animals under current or past milk recording. Solutions for fixed effects from mixed model equations from genetic evaluation such as genetic groups and herds are also stored in their databases. Additionally, the casein genotypes for various variants for specific animals are stored in the database for selection purposes. Casein variants are regarded as markers for various traits of interests in dairy cattle breeding. Similar examples can easily be found in all major livestock breeding organisations around the world, especially also for chickens. This invalidates claims 1di, 1dii and 1diii above, i.e. these claims do not represent novel approaches.

Claim 1e, i.e. *“A method of increasing an animal population's average genetic merit, comprising; a. selecting one or more traits for which an improved genetic merit is desired; e. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to calculate a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits. This claim is odd-formulated in its last part where the claim is to patent a method “wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers”*.

A breeding value for a genetic marker does only exist if the genetic marker has a genetic effect upon the trait of interest. This is the case for intra-genic markers such as e.g. intra-genic SNPs. However, e.g. all microsatellite markers by design are not expressed and would thus be excluded from this claim. We are not sure, whether this is the intention of the authors of this patent application. However, it is not our task to infer the applicants intentions.

Boichard et al. (2002) describe the implementation of marker-assisted genetic evaluation using best linear unbiased prediction followed by marker-assisted selection in French Dairy Cattle. Their paper describes the implementation into breeding practice of the exact principles Monsanto Technology LLC is claiming to be theirs. The approach taken by Boichard et al. is based on Fernando and Grossman (1989). Finally, *applied genetics network*, Davos, Switzerland was contracted by Livestock Improvement Corporation, (LIC), New Zealand in the year 2002 to develop marker assisted BLUP procedures and computer programs suitable for application on LIC's cattle herds. *applied genetics network* has delivered a computer program in December 2003 to LIC suitable for marker-assisted selection using multiple traits, markers and QTL based on iteration on data and variable-block preconditioned conjugate gradient as described in the above mentioned patent application. The computer program was developed in collaboration with Prof. Dr. R.L. Fernando, Department of Animal Sciences, Iowa State University, Ames, IA, USA. As the development of this computer program was connected to a commercial mandate, the procedures cannot be disclosed here. However, Dr Bevin Harris, Livestock Improvement Corporation, New Zealand¹, Prof R. L. Fernando² and Dr. Christian Stricker³, *applied genetics network*, Davos, Switzerland will be able to confirm this information. Claim 1e does therefore not present a novel approach

In conclusion, none of the claims 1a-e represent a new invention. Therefore, we propose that no patent is granted for those claims. Furthermore, claim 1 is central to the present patent application in the sense that, most of the subsequent claims are derived from claim 1. Due to claim 1 not representing a new invention, all subsequent claims mentioned below cannot represent new inventions either. Main reasons supporting this are given below.

2. *The method of 1 further comprising using the calculated EBVs to prepare a breeding plan for the animal population that provides for optimal improvement in the genetic merit of the population.*

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Animal breeding has a long tradition of using calculated EBV to be used in breeding plans. The information that has been used to calculate EBV has evolved from poorly recorded phenotypic observations to well established routine phenotyping combined with pedigree information as well as genotypic information (e.g. casein genotypes). As only one of several examples, the Swiss Red and White Cattle Breeding Association and the Swiss Brown cattle Breeding Association are currently providing internet based breeding plans to their customers using calculated EBVs. Therefore, claim 2 does not present a new invention. Furthermore, it is doubtful whether claim 2 has a sufficient technical character as such which would allow the grant of patent protection.

3. *The method of claim 1 wherein the animal population is a swine herd.*

Due to reasons given against claim 1, claim 3 does not present a new invention. Additionally, Dekkers (2004) explicitly states in his section "Examples of Applications of MAI or MAS" on page E318:

"One of the first examples of use of an LD marker for a quantitative trait was the test for the estrogen receptor gene (ESR; Rothschild et al., 1996; Short et al., 1997), which has been used in several commercial lines to enhance selection for litter size (G. Plastow, personal communication). Plastow et al. (2003) and G. Plastow (personal communication) also reported the use of more than 15 proprietary direct and LD markers (PICmarq) for traits associated with reproduction, feed intake, growth, body composition, and meat quality in pigs."

Thus, claim 3 and claim 1 are not new inventions.

4. *The method of claim 1 wherein the trait is selected from the group consisting of: efficient growth traits, meat quality traits, reproduction traits, and health traits.*

This claim does not present a new invention as selecting for such traits has a long tradition in livestock. Dekkers (2004) in table 1 lists markers for such traits that are exploited by various selection programs.

5. *The method of claim 1 wherein the molecular genetic markers are selected from any polymorphism known to affect expression of themRNA or protein from a gene.*

This claim is not formulated correctly. This claim is not a new invention for the same reasons given in the objection to claim 4 and claim 1.

6. *The method of claim 5 where the polymorphism is selected from the group consisting of: single nucleotide polymorphisms, simple sequence repeats, protein point mutations, and gene isoforms.*

The marker-assisted BLUP methodology presented in the patent application is applicable to all type of marker information, irrespective of it molecular form and/or

whether it is a marker in linkage equilibrium or disequilibrium or locus with a direct effect. This methodology has been publicly available since 1989 (Fernando and Grossmann, 1989). Therefore, claiming a patent for the methodology for a special type of marker information does not present a new invention.

7. The method of claim 3 wherein at least one molecular genetic marker is selected from those markers known to modulate a favorable phenotype.

The same objection as for claim 6 applies.

8. The method of claim 3 wherein at least one of the molecular genetic markers is a marker for selected from the group consisting of: a single nucleotide polymorphism in the porcine PRKAG3 (protein kinase, AMP-activated gamma-3 subunit) gene, and a polymorphism in the porcine melanocortin-4-receptor.

The same objection as for claim 6 applies. Note that Monsanto Technology LLC does not hold a patent related to PRKAG3.

9. The method of claim 3 wherein at least one of the molecular genetic markers is a marker for a single nucleotide polymorphism in the porcine PRKAG3 gene.

The same objection as for claim 6 applies. Note that Monsanto Technology LLC does not hold a patent related to PRKAG3.

10. The method of claim 1 wherein the computer program uses an iteration-on-data (IOD) algorithm and a preconditioned conjugate gradient (PCCG) algorithm to determine the animals' ranks.

Solving systems of equations by iteration on data using preconditioned conjugate gradients has been described before the above mentioned patent application was filed. It was probably first described by Hestenes et al. (1952). More recently Shewchuk (1994) gave an introductory overview. It is a well established mathematical procedure. Genetic evaluation using best linear unbiased prediction is based on the mixed model equations introduced by Henderson (1963). Those linear equations are subsequently solved by iteration on data using PCCG by many if not most organizations involved in routine genetic evaluation in large livestock populations. Tsurata (2001) tested PCCG methodology combined with iteration on data using 16 test situations (various data sets and models). Using molecular genetic information to model an observation in the mixed model equations (to calculate covariance among individuals and/or account for a direct effect of a certain marker genotype) does not change the fact, that still a set of linear equations is solved by methods which have been introduced prior to this patent application. Therefore, claim 10 does not present a new invention.

11. The method of claim 10 wherein the PCCG algorithm is a variable-size block-diagonal preconditioning algorithm.

The same objection as for claim 10 applies. For example, Shewchuk (1994) shows, that for efficient preconditioning, the preconditioner matrix should be preferably as close as possible to the coefficient matrix but additionally it needs to be easy to invert. This is best achieved by a diagonal or block-diagonal structure with blocks referring to correlated random effects. For multi-trait models, this is best achieved by ordering equations such that traits within the correlated random effects of the model are blocked. For example, in a two trait model with the random effect 'animal', block size would be two, whereas in a two trait model with the random effect 'animal' and a random maternal effect, block size would be four. PEST (Groneveld, 1990) uses this variable-size blocking scheme for Gauss-Seidel iterations. Lidauer et al. (1999) discuss block-preconditioning in the context of iteration on data. As the blocking scheme depends upon the models applied to the data, variable-size block preconditioning is an obvious technique in PCCG. applied genetics network has incorporated this technique in its MABLUP computer program that has been delivered to Livestock Improvement Corporation, New Zealand in 2003. Therefore, claim 11 does not represent a new invention.

12. The method of claim 1 wherein the output of the computer program further comprises results that indicate the informativeness of one or more of the selected molecular genetic marker for at least one quantitative trait locus (QTL) and/or a calculation of the genetic closeness/proximity of one or more molecular markers to at least one QTL.

Since claim 1 does not represent a new invention, claim 12 does also not represent a new invention as it is based on claim 1. Calculating the informativeness of molecular genetic markers with respect to a QTL is common practice in QTL mapping in animals and humans (see e.g. Ott, 1999: chapter 5). Calculating the genetic closeness/proximity of one or more molecular markers to at least one QTL is commonly referred to as linkage analysis. Such analysis originated in human genetics decades ago (c.f. Ott, 1999 for an overview). It thus cannot be taken as a new invention.

13. The method of claim 12 wherein the molecular genetic markers having the highest degree of informativeness and/or closeness for at least one QTL are identified.

For the same reason as given against claim 12, this does not represent an new invention.

14. The method of claim 1 wherein the computer program utilizes a scripting feature to improve the ease of user interface.

There is nothing to say against protecting the specific scripting feature or program that was invented by Monsanto Technology LLC for the computer program performing the tasks mentioned in claim 1-15. However, to assess whether such a specific scripting program contains a novel approach is only possible, when the specific features of such a scripting program are disclosed. Trying to patent scripting features in general is almost ridiculous, given that the invention of the scripting language Perl in the year 1987 (<http://history.perl.org/PerlTimeline.html>). Therefore, claim 14 does not represent a new invention.

15. The method of claim 1 wherein the selected molecular genetic markers comprise a marker haplotype.

Claim 1 comprises the use of one or several molecular genetic markers. Correctly considering several markers jointly requires to account for the gametic phase of a multi-locus genotype. The phase of a multi-locus genotype is formed by its two haplotypes. Therefore claim 1 includes molecular genetic haplotypes already. Therefore, for the same reasons as claim 1 is not a new invention, claim 15 is not a new invention either.

16. A system for increasing an animal population's average genetic merit for at one or more selected traits, the system comprising: a. a computer; b. a computer accessible database providing data on one or more quantitative trait locus (QTL) for each selected trait; c. a computer accessible database providing data, for animals in population, for three or more molecular genetic markers for each selected QTL for each selected trait; d. a computer accessible database providing pedigree data for animals in the population; e. optionally, a computer accessible database providing individual data for each animal in the population for at least one fixed effect; f. a computer executable program capable of simultaneously evaluating the data in all databases and ranking the animals in the population according to their respective estimated breeding value for each of the selected traits; g. a user interface including a data entry system, said user interface coupled to said computer and configured to allow the user to instruct the computer to access the available databases and use the computer program to generate output that includes a ranking of the animals according to their estimated breeding values and/or their individual estimated breeding values.

Given that breeding organizations involved in managing large livestock populations all around the world are already using computers to store and retrieve phenotypic and genetic data including pedigree information as well as breeding values and solutions of effect levels used in modeling phenotypic observations, in large scale databases, claim 16 is, moderately speaking, outdated. Due to this, no references to such breeding organizations are given, but can be provided upon request.

17. *The system of claim 16 wherein the animal population is a swine herd.*

For the same reasons given in the objection against claim 16, claim 17 does not represent a new invention, as there are numerous breeding organizations working with swine populations already doing just what is listed in claim 16.

18. *The system of claim 17 wherein at least one of the molecular genetic markers is selected from the group consisting of markers for the porcine PRKAG3 gene and the gene encoding the melanocortin-4-receptor.*

This claim would prevent anyone else of storing and retrieving information related to the porcine PRKAG3 gene and the gene encoding the melanocortin-4-receptor in data bases using computers. Note that Monsanto Technology LLC does not hold a patent related to PRKAG3. Additionally, this claim is based on claim 17. Therefore, claim 18 does not represent a new invention.

19. *The system of claim 17 wherein at least one of the molecular genetic markers is a marker for a single nucleotide polymorphism in the porcine PRKAG3 gene.*

This claim would prevent anyone else of storing and retrieving information related to a SNP in the porcine PRKAG3 gene in data bases using computers. Note that Monsanto Technology LLC does not hold a patent related to PRKAG3. Additionally, this claim is based on claim 17. Therefore, claim 18 does not represent a new invention.

20. *The system of claim 17 wherein the selected molecular genetic markers comprise a marker haplotype.*

This claim does not present a new invention for the same reasons given in the objection against claim 15, 16, and 17.

21. *A system for identifying the molecular genetic marker (s) having the highest degree of informativeness for one or more selected quantitative trait locus (QTL), the system comprising : a. a computer; b. a computer accessible database providing individual data, for animals in population, for three or more molecular genetic markers for each selected quantitative trait locus; c. a computer executable program capable of simultaneously evaluating the data in all databases and determining the relative informativeness for each of the molecular genetic markers for which data is provided; d. a user interface including a data entry system, said user interface coupled to said computer and configured to allow the user to instruct the computer to access the available databases and use the computer program to generate output that includes a indication of the informativeness of each molecular genetic marker for which data was provided.*

For the same reasons given against claim 12 and 13, this claim does not present a new invention. Additionally, data about the informativeness of molecular markers related to QTL have been stored and retrieved from databases in human genetics long before the present patent application has been filed. In the context of the human genome project and all the projects in human genetics trying to map disease QTL, appropriate references can be found in the proceedings of the meetings of the American Society of Human Genetics from the last 2-3 decades.

22. *The system of claim 21 wherein the quantitative trait locus is selected from any locus known to be associated with a known trait.*

This claim is already covered by claim 21, stating “A system for identifying the molecular genetic marker (s) having the highest degree of informativeness for one or more selected quantitative trait locus (QTL), ...”, i.e. claim 21 does not specify of what nature the informativeness of the genetic marker(s) is/are. Therefore, association between a marker and a trait is included. Therefore, claim 22 is not presenting a new invention for the same reason as claim 21.

23. *The system of claim 21 wherein the quantitative trait locus is selected from any locus for traits selected from the group consisting of efficient growth traits, meat quality traits, reproduction traits, and health traits.*

The objection against claim 21 invalidates this claim also.

24. *The system of claim 21 further comprising providing computer accessible database (s) containing individual data for animals in the population for at least one fixed effect; wherein the computer executable program is capable of simultaneously evaluating the data in all provided databases and ranking the animals in the population according to their respective estimated breeding value for each of the selected traits.*

The objection against claim 21 invalidates this claim also. This claim basically includes the core tasks of today's breeding organizations in livestock, as they have been performed over years.

25. *The system of claim 21 wherein the selected molecular genetic markers comprise a marker haplotype.*

For the same reasons given against claims 15, 16, 17 and 20, this claim does not present a new invention.

26. *A method of identifying the molecular genetic marker (s) having the highest degree of informativeness for at least one quantitative trait locus (QTL), the method comprising. a. selecting at least one trait for which an informative molecular genetic is desired; b. providing database (s) comprising data for one or more quantitative trait locus (QTL) for each selected trait, for a plurality of animals in an animal population; c. providing database (s) comprising data for three or more molecular genetic markers for each selected QTL for each selected trait, for a plurality of animals in an animal population; d. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from all provided databases to calculate the informativeness of the provided markers; e. identifying the marker (s) that is/are most informative for the selected trait (s).*

This claim is ambiguous, in claim 26a it is not clear what the term ‘informative molecular genetic’ is referring to. Claims 26b-c, e are included in claims 16 and 21. Therefore, they are not presenting a new invention for the reason given in the objection against those claims. Claim 26d refers to marker-assisted BLUP, already included in claim 1. It therefore does not present a new invention.

27. *The method of claim 26 further comprising providing databases comprising: i. data providing the pedigree for the animals in the animal population; and ii. optionally, data for one or more fixed effects for the animals in the population; wherein the method also further comprises using the computer program capable to performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from all provided databases to determine the informativeness of the selected markers and to calculate a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected traits.*

This claim is composed of previous claims, mainly claim 1, 16 and 26. It has been shown in the objection against those claims that they do not present a new invention. Therefore, this claim 27 does not present a new invention, either. Particularly, it is not new to combine the elements which are already in the public domain.

28. *A method of evaluating an animal population's average genetic merit for a defined set of traits, wherein the defined traits comprise the animal's status for one or more quantitative trait locus (QTL) and at least three molecular genetic markers for each QTL, the animal's pedigree; the method comprising: a. selecting one or more traits for evaluation; b. providing databases comprising: i. data for one or more quantitative trait loci (QTL) for the animals in the population ii. data for three or more selected molecular genetic markers for each QTL, for each*

selected marker for the animals in the population; iii. data providing the pedigree for the animals in the population; c. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to produce a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits; d. evaluating the EBVs to determine the animal population's average genetic merit for the defined set of characteristics.

This claim refers to the calculation of the genetic merit of a population for a defined set of traits. The genetic merit of a population can be defined as the aggregation of the genetic merit of each member of the population. If it is assumed that the genetic merit of each individual can be added to obtain the genetic merit of the population, then claim 28 is entirely contained in previous claims, e.g. claim 1, 16, 26, 27, except for the fact that claim 28 refers to the average genetic merit of a population. However, no indication is given w.r.t. the details of the method how this average genetic merit is calculated. Therefore, the method of calculating such an average genetic merit does not represent a new invention, neither do claims 28a-d as previously stated in the objection against claims 1, 16, 26, and 27, for example. Moreover, it is also doubtful for other reasons whether this claim is patentable since in view of the lacking details of the method how this average genetic merit is calculated, it seems not possible to put this claim into practice without further information.

29. A method of identifying optimal breeding pairs in an animal population to improve a previously selected characteristic in the population comprising: a. selecting one or more traits for improvement; b. providing computer readable data for one or more quantitative trait locus for the selected traits; c. providing computer readable data for at least three molecular genetic markers for each QTL for each selected trait; wherein the data indicates the genetic makeup of animals in the population, with respect to the molecular genetic marker; d. providing computer readable data representing the pedigree for animals in the population; e. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided data to produce a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits; f. using the animals' ranks to identify the optimal breeding pairs in the population.

Identifying optimal breeding pairs is a central task in animal breeding. Engeler (1996) has developed a computer program suited to identify optimal breeding pairs w.r.t. to their EBV and/or phenotypic records at multiple traits. He also gives an overview over computer programs suitable for exactly the tasks listed in claim 29. In the year 2000, the Swiss Brown Cattle Breeders' Federation and the Swiss Red and White Cattle Breeding Association have implemented the approach of Engeler (1996) in a web-based application. Claim 29 does therefore not represent a new invention.

30. *The method according to any one of claims 26 to 29 wherein the selected molecular genetic markers comprise a marker haplotype.*

This claim does not represent a new invention due to reasons given in the objection against claim 15, 16, 17, 20 and 25.

43. *A method of increasing an animal population's average genetic merit, comprising; a. selecting one or more traits for which an improved genetic merit is desired; b. selecting one or more quantitative trait locus (QTL) for each selected trait; c. selecting one or more molecular genetic markers of interest for each QTL for each selected trait; d. providing databases comprising : i. genotype data for three or more molecular genetic markers for each selected trait, for a plurality of animals in the population; ii. data providing the pedigree for each animal in the population; iii. optionally, data for one or more fixed effects; e. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to calculate a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits.*

This claim refers to increasing the average genetic merit of a population. This claim is comprised entirely in claims 1, 16, 26, 27 and 28. Furthermore, increasing the genetic merit of a population is the obvious motivation of breeding organizations in general. Claim 43 does therefore not present a new invention.

44. *A system for increasing an animal population's average genetic merit for at one or more selected traits, the system comprising: a. a computer; b. a computer accessible database providing data on one or more quantitative trait locus (QTL) for each selected trait; c. a computer accessible database providing data, for animals in population, for one or more molecular genetic markers for each selected QTL for each selected trait; d. a computer accessible database providing pedigree data for animals in the population; e. optionally, a computer accessible database providing individual data for each animal in the population for at least one fixed effect; f. a computer executable program capable of simultaneously evaluating the data in all databases and ranking the animals in the population according to their respective estimated breeding value for each of the selected traits; g. a user interface including a data entry system, said user interface coupled to said computer and configured to allow the user to instruct the computer to access the available databases and use the computer program to generate output that includes a ranking of the animals according to their estimated breeding*

values and/or their individual estimated breeding values.

This claim refers is composed of previous claims, specifically claim 21, 26, 27, 28, 29, 43 and 44. For the reasons given in the objection to those claims, it does not present a new invention.

45. *A method of identifying optimal breeding pairs in an animal population to improve a previously selected characteristic in the population comprising: a. selecting one or more traits for improvement; b. providing computer readable data for one or more quantitative trait locus for the selected traits; c. providing computer readable data for one or more molecular genetic markers for each QTL for each selected trait; wherein the data indicates the genetic makeup of animals in the population, with respect to the molecular genetic marker; d. providing computer readable data representing the pedigree for animals in the population; e. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided data to produce a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if provided, quantitative traits; f. using the animals' ranks to identify the optimal breeding pairs in the population.*

This claim is virtually identical to claim 29 and represents therefore no new invention for the same reasons given in the objection against claim 29.

(46, listed last) *A method of evaluating an animal population's average genetic merit for a defined set of traits, wherein the defined traits comprise the animal's status for one or more quantitative trait locus (QTL) and at least one or more molecular genetic markers for each QTL, the animal's pedigree; the method comprising: a. selecting one or more traits for evaluation; b. providing databases comprising: i. data for one or more quantitative trait loci (QTL) for the animals in the population ii. data for one or more selected molecular genetic markers for each QTL, for each selected marker for the animals in the population; iii. data providing the pedigree for the animals in the population; b. using a computer program capable of performing a marker assisted best linear unbiased prediction to simultaneously analyze the data from the provided databases to produce a ranking of the animals; wherein the animals are ranked according to their estimated breeding value (EBV) for the selected molecular genetic markers and, if*

provided, quantitative traits; d. evaluating the EBVs to determine the animal population's average genetic merit for the defined set of characteristics.

This claim is virtually identical to claim 28 and represents therefore no new invention for the same reasons given in the objection against claim 28.

Final Remarks

The above mentioned patent applications is written in an extremely broad sense. Granting this patent would mean that European breeding organizations would no longer be able to use well established procedures related to routine genetic evaluation such as storing and retrieving phenotypic and genetic data in databases, using such information to evaluate and improve the genetic merit of an individual or population by methods based on solving a set of linear equations with commonly available algorithms without appropriate licensing. Furthermore, designing breeding plans and incorporating them in the breeding population would be restricted in the same sense. Marker-assisted selection in general would no longer be possible without proper licensing. The competition in the market place would be distorted in a way which is not justified by patent law. We have shown that all those technologies have been in place prior to the above mentioned patent application. Therefore, for all the claims objected herein, we cannot see reasons for a patent to be granted.

Furthermore, the above mentioned patent applications is poorly written in the sense that many claims are very difficult to understand it their implications. Some of them could not be put into practice without further information. We are convinced that a patent should be granted for a specific new invention and not for an exhaustive list of common but poorly described animal breeding technologies.

Date / Place: _____

Hans Künzi
Director Association of
Swiss Cattle Breeders

References

- Boichard, D. et al. 2002. Implementation of marker-assisted selection in French Dairy Cattle. Proc. of 7th World Congress on Genetics Applied to Livestock Production. August 19-23, 2002. Montpellier, France.
- Dekkers, JCM 2004. Commercial application of marker- and gene-assisted selection in livestock: Strategies and lessons. *J. Anim. Sci.* 82 (E. Suppl.): E313–E328; <http://www.asas.org/symposia/04esupp/E313.pdf>
- Engeler, R. 1996. Optimale Kombination von Leistungseigenschaften in der Rindviehzucht. Ph.D. Thesis Swiss Federal Institute of Technology, Switzerland, Diss ETH Nr. 11638.
- Fernando, R.L. 2004. Incorporating molecular markers into genetic evaluation, Session G6.1, Proc. 55th Meeting of the European Association of Animal Production EAAP, Bled Slovenia.
- Fernando, R.L. and M. Grossman 1989. Marker assisted selection using best linear unbiased prediction. *Genet. Sel. Evol.* 21, 467-477.
- Groeneveld, E. 1990. PEST User's Manual. Available at Inst. Anim. Husbandry and Behaviour, Fed. Agric. Res. Centre (FAL), 31535 Neustadt 1, Germany. <http://www.tzv.fal.de/~eg/>
- Henderson, C. R. 1963. Selection index and expected genetic advance. In: *Statistical Genetics and Plant Breeding*, Hanson, W. D. and H. F. Robinson, eds., 141-163, Publication 982, National Academy of Sciences, National Research Council.
- Hestenes, M.R. and Stiefel, E. 1952. Methods of Conjugate Gradients for Solving Linear Systems, *Journal of Research of the National Bureau of Standards* 49, 409–436.
- Johnson, D.L., Stricker, C. Fernando, R.L. and Harris, B.L. 2005. Moving from BLUP to Marker-Assisted BLUP for Genetic Evaluations. Proc. 2005 Interbull Meeting, Uppsala Sweden, June 2-4, Bulletin 33.
- Lidauer, M. Stranden, I., Mäntysaari, E.A. Pösö, J. Kettunen A. 1999. Solving large test-day models by iteration on data and preconditioned conjugate gradient. *J. Dairy Sci.* 82, 2788-2796.
- Ott, J. 1999. *Analysis of Human Genetic Linkage*, Third Edition. The John Hopkins University Press, Baltimore and London. ISBN 0-8018-6140-3.
- Plastow, G., S. Sasaki, T-P. Yu, N. Deeb, G. Prall, K. Siggens, and E. Wilson. 2003. Practical application of DNA markers for genetic improvement. Pages 151–154 in Proc. 28th Annu. Mtg. Natl. Swine Improve. Fed., Iowa State Univ., Ames.
- Shewchuk, J.R. 1994. *An Introduction to the Conjugate Gradient Method Without the Agonizing Pain*. Edition 1 1/4. School of Computer Science Carnegie Mellon University

Pittsburgh, PA 15213. <http://www.cs.cmu.edu/~quake-papers/painless-conjugate-gradient.pdf>

Tsurata, S., Misztal, I., Strandén, I. 2001. Use of the preconditioned conjugate gradient algorithm as a generic solver for mixed-model equations in animal breeding applications. *J. Anim. Sci.* 79, 1166-1172.