On the Robustness of SNPs Filtering using Computational Intelligence

Bruno Zonovelli, Carlos Cristiano Hasenclever Borges
Federal University of Juiz de Fora
Computer Science Department
Juiz de Fora, Brazil
zanova@gmail.com, cchborges@ice.ufjf.br

Wagner Arbex*
Federal University of Juiz de Fora and Brazilian
Agricultural Research Corporation
Juiz de Fora, Brazil
wagner.arbex@embrapa.br

* corresponding author

Abstract — **This work uses a filter based on neural networks to verify the mismatches in two Arabidopsis thaliana germplasm. Aiming to demonstrate the robustness and adaptability of the filter it will be applied in a reuse model context. The neural network filter previously defined and performed using the genome of an animal of the species Bos Taurus is used maintaining the main parameterization pre-defined to identify the SNPs on the mismatches detected in the reassembled germplasm. The experiments with the adapted filter in the new genome indicate that the quality and level of SNPs detection are preserved despite of the lack of a training process for this specific data.**

Keywords - Bioinformatics; Genomic DNA; SNP Filtering; Computational Intelligence; Neural Network; NeuroSNP.

I. INTRODUCTION

The correct identification of single nucleotide polymorphisms (SNP) is an important issue to understand variability in a population of specie allowing to study its consequences. However, for correct identification of SNPs candidates efficient filters are mandatory for quality on detection. The SNP filtering applied on data obtained by next generation sequencing (NGS) is a challenge due to its own characteristics. In this way, new developments are necessary to obtain an efficient and robust search for SNPs detection. In this respect, a study developed by these same authors [1] introduced the NeuroSNP, a filter tool based on neural networks attesting the possibility of the use a computational intelligence tool as technique for SNPs filtering.

The main goal of this work is to use a neural network trained previously for a bovine genome [1] to filter the SNPs of a new genome in a context of model reuse. The objective is evaluate the robustness and adaptability of the machine learning filter developed regardless the type of data it is applied. For this purpose the genome of Arabidopsis Thaliana species is used.

II. THE NEUROSNP FILTERING

The NeuroSNP filtering [1] was developed using an artificial neural networks model. The input variables are intrinsically based on the output variables of MAQ software [2] that contains its own filter. In this way, the NeuroSNP configuration was defined with ten neurons in the input layer, a hidden layer with twenty neurons and a binary output layer. The Resilient Propagation (RPROP) learning algorithm was applied on training phase to construct a resilient network. The model was encoding using the library Fast Artificial Neural Network (FANN) [3]. The parameters for NeuroSNP execution are listed in Table 1.

Table 1: Parameters of NeuroSNP

Parameters	Description
-n	Output file of training the network.
-o	Output file of NeuroSNP
-d	Source file of the SNP - output file MAQ.
-r	Restriction (0 - Low, 1 - High, 2 - Medium).

The binary filter encoded in MAQ software classifies the candidate SNP as 0 or 1 if the SNP is true or false positive, respectively. Thus, the usually used function at neural network it would the step function. However, the developed network achieved better results using the sigmoid function (Figure 1) as output. This function classifies the SNPs in the range [0, 1] instead of binary values. That singular difference allows the inclusion of an important feature in the NeuroSNP structure defined as restriction. The restriction parameter has as objective to set the output of the sigmoid function as binary value with different adjustments depending on a discrete value defined by the user. Thus the neural network NeuroSNP can use this parameter to refine the performance for different kinds of data.

Three restrictions, **Low**, **Medium** and **High** were defined. The **Low** restriction classifies any SNPs as true SNP if the output value is greater than 0. The **Medium** restriction is similar to the step function, i.e., all SNPs with output value greater than 0.5 is rated as true. The **High** restriction only classifies SNPs as true if the output value is equal to 1. Figure 1 depicted these restrictions in the sigmoid function.

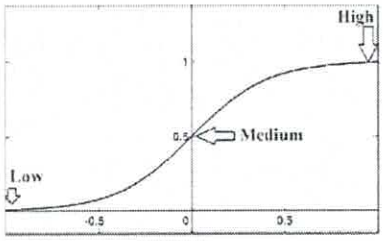

Figure 3: Sigmoid functions and restrictions.

III. IDENTIFICATION OF FALSE POSITIVES

The task of assembly a complete genome embodies the process of sequencing, alignment and assembly of reads. In each of these steps an error rate is generated. Thus, in the SNPs identification phase this error can induce the filter to interpret the mismatches as a SNP. In the discovery stage any difference between the sequences is a mismatch with some of these differences being a SNPs and others no. Despite the difference, define when this mismatch is or not a SNP is a complex task. Usually, this definition is committed to a filtering step. Regarding the NGS platforms, the introduced errors remain in the range of 0.1% up to 1% [4].

The process evolves by the aligning of two sequences with the reference genome to generate consensus. The alignment and assembly software identifies a mismatch in the first positions of the fragment. However the obtained alignment may not be the best for this fragment. This situation typically occurs when short reads are used, which is common for NGS platforms data. The mismatch generated by the adopted alignment could be an error in the sequencing step, or a real SNP.

The Figure 2 shows the correct alignment between fragments, generating true SNPs.

Figure 4: True SNPs generated by the alignment step.

The Figure 3 indicates an example of a mismatch generated by an alignment error resulting from sequencing mistake [5].

Another possible case depicted in Figure 4 the alignment is corrected. However the reads present low quality.

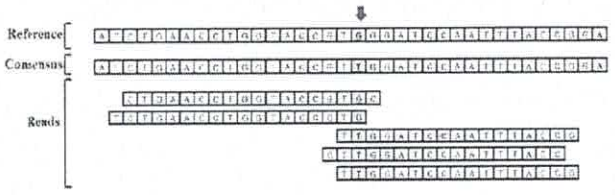

Figure 2: False positives generated by the alignment step.

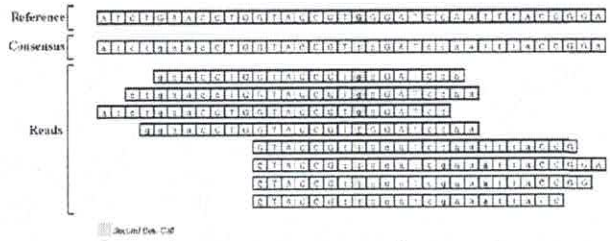

Figure 1: False positive generated by low quality.

The main question to be evaluated is ensure if a mismatch is a SNP or represents an error. Usually a filter is the responsible for this task. Using some strategy the filter attempts to classify mismatches as SNPS or sequencing error. When an error is reported as SNPs a false positive is obtained. Despite the NGSs platforms errors could be considered low (0.1% up to 1%), the genome size usually is huge with millions of base pairs. Thus, the relative error is small, but the absolute value of mismatch errors for the complete genome could be very large. Therefore, an efficient filtering tool is mandatory for the purpose of SNP detection on high performance.

IV. DATABASE MODELS

An attempt to develop a supervised learning specific for SNPS filtering must necessarily defines a strategy for the construction/obtainment of the training database with the determination of instances class accurately. This is a hard task since for this kind of problem a well-defined base of SNPs for each genome is not trivial to obtain. Besides, the data for the sequencing error class do not have a prior pattern to be generated. Usually a filtering problem is considered as one-class classification problem when tackled by means of machine learning tools. So, to construct the databases for the SNPs class and sequencing errors class two strategies are defined:

1. By using a pre-filter for determining the classes (First Model);
2. By building specific data sets based on pre-defined rules aiming to maximize the potential of generalization of the supervised classification tool (Second Model).

Following, the construction of database for the two models are described in details.

B. *First Model*

In this case, the data for the two classes are obtained directed of the archives generated for a standard method: the archive of detected mismatches and the archive of filtering these mismatches

1. Dataset used was extracted from the output files of the MAQ software [2].
2. These steps was used the reassembled genome Bos Taurus [6].
3. The first file is derived from the discovery step (mismatches detected).
4. The second file (true SNPs) is obtained from the filtering step.
5. First file has about 7 million SNPs and the second contains about 2 million.

These two sets are used for the training phase of the neural network to be generated.

C. *Second Model*

For the second model, more restricted rules are used aiming to separate clearly the two classes of SNPs and false positives. The rules are based on modifications of the rules used by the filter of the MAQ software defining sets of high and low trusted SNPs. The rules, applied on the files generated for the First Model are:

1. SNPs with high trust (about 429,078 SNPs):
   1. covering greater > 6;
   2. Phred-like > 20;
   3. Quality and mapping quality on the flank of 6 > 50.
2. SNPs with low trust (about 1,821,527 SNPs):
   1. Same parameters in the group with high trust.
   2. Pick the SNPs that have at least one parameter equal 0.

These two files are used for training phase as previous model. It is interesting to emphasize that both strategies suffer with problems relating to noise in class determination (SNPs or false positive) of each candidate. The rules for the Second Model are more rigorous trying to diminish this effect. The evaluation of each model in previous work [1] indicates a better potential for Second Model when the filter is applied in the same genome used for training the NeuroSNP filtering.

V. Obtaining Data by Reassembly

The processes of discovery and filtering are always executed after genome assembling. For that it is necessary to execute this phase of the project using MAQ software. It is worthwhile to stand out that the genome assembling could be very extensive. Aiming to test NeuroSNP filter in genomes different of *Bos* Taurus genome two distinct germplasm were reassembled using the MAQ software. The stage of discovery generates the necessary file for create the set of false positives. The SNPfilter, filter included in MAQ software generates the file used to create the set of true SNPs in both models.

The first genome analyzed by NeuroSNP filter was an animal of the species Bos Taurus, Fleckvieh breed. The experiments carried out indicate that the NeuroSNP filter improves the results obtained only using the SNPfilter coupled in MAQ software [1]. The tests accomplish in this work are based on the genome of Arabidopsis Thaliana species, which was the first plant genome sequenced with a large volume of research over its data. Its genome is diploid with five chromosomes and about 125 million base pairs. Two different germplasm, the TSU-1 and BUR-0 were reassembled, aligned to the reference genome TAIR10 [7].

VI. Odds Ratio – OR

A difficult task is to asseverate that the results of filtering process are reliable, i.e., if the filter indicates that a mismatch is a SNP it is not ease to confirm directly the veracity of this information. An indirect measure namely, Odds Ratio (OR), will be used to evaluate the results generated by the filters. For the SNPs filtering problem, the OR measure indicates the change in probability of finding a valid alignment within a sample of filtered SNPs, compared with other set of unfiltered sample. Following, the description of the measure using the sets of filtered and unfiltered data:

A_t = Sample of unfiltered SNPs or total.

A_{ta} = Number of total alignments found in A_t in relation to dbSNP base.

A_f = Filtered sample (SNPfilter or NeuroSNP).

A_{fa} = Number of alignments (SNPs) found in A_f in relation to dbSNP base.

The following rates define the OR:

$$r(A_t) = \frac{A_{ta}}{A_t - A_{ta}}$$

$$r(A_f) = \frac{A_{fa}}{A_f - A_{fa}}$$

$$\mathrm{OR} = \frac{r(A_t)}{r(A_f)}$$

The dbSNP database is the reference used to attest the veracity of the SNPs detected. Greater values of OR indicates that the filter is more efficient, augmenting the number of true SNPs detected in relation to dbSNP database. The value adopted for the analysis considerer a confidence interval (CI) of 95% for the standard error (SE).

$$SE = \sqrt{\frac{1}{A_t - A_{ta}} + \frac{1}{A_{ta}} + \frac{1}{A_f - A_{fa}} + \frac{1}{A_{fa}}}$$

$$CI^p = \exp(\ln(OR) + 1.96 \times SE)$$

$$CI^n = \exp(\ln(OR) - 1.96 \times SE)$$

$$CI = [CI^n, CI^p]$$

VII. Tests with BUR-0

Each model was run 10 times, where each run get different values for the training error and testing. Thus to facilitate analysis of the results, the selected networks received the following names: NeuroSNP1.A to network with the lowest and the first model NeuroSNP1.B for with the greatest error. The NeuroSNP2.A to network with the lowest and the second model NeuroSNP2.B for the greatest error.

B. Results Obtained by First Model

Table 2 shows the results of the First Model, where is possible to see that none of the two networks could overcome the result obtained with SNPfilter. The behavior of the First Model remains similar to observed in the bovine genome, i.e., the model maintains its pattern for the new data set. The CIs obtained by the ORs are greater than the value observed in the bovine genome, but the range is still small demonstrating that the ORs kept accurate.

The variation in the value of the ORs for the second genome is small. However, its value still maintains inconstant as in bovine genome. Although the first model is not the best between both, the maintenance of behavior demonstrates that it is robust, despite not being the most effective. Table 2 displays the result of the ORs obtained by NeuroSNP applied on bovine genome compared with that obtained in the germplasm BUR-0. As can be seen the behavior of the filter is similar, with mode effectiveness for the current germplasm.

Table 2: Results for SNPfilter and NeuroSNP using the First Model with SNPS of germplasm BUR-0 and a comparison with Bos Taurus.

BUR-0

	Arabidopsis thaliana				Bos Taurus	
	SNPs	Alignments	OR	CI	OR	CI
MAQ	1,135,193	921	-	-	-	-
SNPfilter	544,881	832	1.883	1.715 - 2.069	5.375	5.356 - 5.393
NeuroSNP1.A						
High	353,029	547	1.911	1.719 - 2.125	5.030	5.012 - 5.048
Medium	510,646	736	1.778	1.613 - 1.959	4.303	4.289 - 4.317
Low	681,773	870	1.574	1.434 - 1.726	3.513	3.502 - 3.523
NeuroSNP1.B						
High	189,486	250	1.627	1.415 - 1.871	6.067	6.043 - 6.091
Medium	550,193	798	1.789	1.627 - 1.967	4.840	4.823 - 4.856
Low	751,417	842	1.382	1.258 - 1.517	3.471	3.461 - 3.481

The increasing in CI interval is explained by the difference in the size of the number of SNPs and the total number of alignments discovered. In the bovine genome the total number of SNPs detected is 2 to 3 times greater than the number of alignments, while in the germplasm of this BUR-0 this value is 600 to 850 times higher.

C. Results Obtained by Second Model

Table 3 shows the results obtained by the NeuroSNP using the Second Model. As observed in the bovine genome, this model remained a stable behavior, obtaining values higher for OR than SNPfilter except for NeuroSNP 2.B where low restriction is settled. The model behavior was close to that obtained for the bovine genome, indicating that the reuse is possible for SNPs filtering with other genomes. The efficiency was preserved in the model reuse process with results with a behavior very similar to that obtained in the bovine genome.

As seen previously the bovine genome, NeuroSNP 2.B has a larger population than NeuroSNP 2.A, but with a smaller variation in OR. The variation in population size can be an interesting feature for the researcher. As observed in the First Model, the ICs have a greater variation in the bovine genome, and again it can be explained by the difference between the sample size and the number of SNPs alignment, which in this model is 500 to 650 times higher.

Table 3: Results for SNPfilter and NeuroSNP using the Second Model with SNPs of germplasm BUR-0 and a comparison with Bos Taurus.

BUR-0

	Arabidopsis thaliana				Bos Taurus	
	SNPs	Alignments	OR	CI	OR	CI
MAQ	1,135,193	921	-	-	-	-
SNPfilter	544,881	832	1.883	1.715 - 2.069	5.375	5.356 - 5.393
NeuroSNP2.A						
High	295,959	576	2.402	2.164 - 2.665	7.399	7.322 - 7.477
Medium	416,194	767	2.274	2.066 - 2.503	7.119	7.065 - 7.174
Low	454,620	785	2.130	1.937 - 2.343	6.880	6.836 - 6.918
NeuroSNP2.B						
High	142,681	265	2.292	1.999 - 2.627	6.207	6.109 - 6.307
Medium	302,030	545	2.226	2.002 - 2.475	6.883	6.832 - 6.935
Low	476,529	681	1.762	1.596 - 1.946	6.042	6.015 - 6.069

The Second Model presents, again. more effectiveness, even when presented to data from a new genome. The networks of the Second Model can be descripted with informative and restrictive characteristics. Therefore variations in the restrictions of sigmoid function generate populations with different sizes, but with similar ORs values. These features indicate that the Second Model is more robust and effective.

D. Considerations

The Second Model showed better indices between the two models studied, being the best alternative for SNPs filtering. The results obtained with the introduction of a new genome indicates that the filtering based on neural networks is robust and can be used as complementally filter to work together with the traditional filters adopted as SNPfilter of MAQ software.

VIII. Tests with TSU-1

The second germplasm analyzed is the TSU-1 following the standards steps performed to bovine genome and germplasm BUR-0. In the discovery phase 1,025,908 SNPs are detected, with 460,140 SNPs obtained after the filter application.

B. Results Obtained by First Model

Table 4 shows the results obtained with NeuroSNP for the First Model. As happen in previous genomes, filtering with NeuroSNP obtained ORs worse than SNPfilter. The behavior of the First Model remains similar to both genomes analyzed. The First Model indicates that even though it is not the most effective it is robust. The CIs calculated have higher values than the bovine genome, however, as in the BUR-0 germplasm, the difference between the sample size of SNPs and the number of alignments is high (600 to 830 times higher for this model).

Table 4 displays the comparison between the ORs obtained in the bovine genome and germplasm TSU-1. For the First Model the results are close, with the NeuroSNP 2.B presenting a relative difference between the variations of ORs.

Table 4: Results for SNPfilter and NeuroSNP using First Model with SNPS of germplasm TSU-1 and a comparison with Bos Taurus.

TSU-1						
	Arabidopsis thaliana				Bos Taurus	
	SNPs	Alignments	OR	CI	OR	CI
MAQ	1,025,908	878	-	-	-	-
SNPfilter	460,140	750	1.906	1.729 - 2.101	5.375	5.356 - 5.393
NeuroSNP1.A						
High	284,015	455	1.873	1.673 - 2.098	5.030	5.012 - 5.048
Medium	429,476	658	1.791	1.619 - 1.982	4.303	4.289 - 4.317
Low	582,256	780	1.566	1.422 - 1.725	3.513	3.502 - 3.523
NeuroSNP1.B						
High	135,773	165	1.420	1.203 - 1.678	6.067	6.043 - 6.091
Medium	459,968	716	1.820	1.649 - 2.009	4.840	4.823 - 4.856
Low	648,088	765	1.380	1.252 - 1.520	3.471	3.461 - 3.481

C. Results Obtained by Second Model

The experiments for this model have the results presented in Table 5. As in previous genomes, this model obtained better results in both networks. Exception is the NeuroSNP 2.B, using high constraint. The model conserved his performance as well as the population variation between NeuroSNP 2.A and the NeuroSNP 2.B, being more restrictive and informative than the SNPfilter.

The values of the CIs obtained by the Second Model networks are larger than the bovine genome, but keep a similar behavior to that encountered in germplasm BUR-0. Likewise, the difference between sample size and the number of SNPs alignments is high for this model (500 to 650 times higher). The behavior is also maintained when compared with the ORs values in relation to the bovine genome as can be seen in Table 5.

Table 5: Results for SNPfilter and NeuroSNP using Second Model with SNPs of germplasm TSU-1 and comparison with Bos Taurus.

TSU-1						
	Arabidopsis thaliana				Bos Taurus	
	SNPs	Alignments	OR	CI	OR	CI
MAQ	1,025,908	878	-	-	-	-
SNPfilter	460,140	750	1.906	1.729 - 2.101	5.375	5.356 - 5.393
NeuroSNP2.A						
High	267,469	548	2.397	2.154 - 2.667	7.399	7.322 - 7.477
Medium	364,580	692	2.220	2.009 - 2.453	7.119	7.065 - 7.174
Low	402,649	703	2.042	1.849 - 2.255	6.877	6.836 - 6.918
NeuroSNP2.B						
High	118,335	233	2.303	1.993 - 2.661	6.207	6.109 - 6.307
Medium	255,114	473	2.169	1.939 - 2.425	6.883	6.832 - 6.935
Low	401,684	612	1.781	1.607 - 1.975	6.042	6.015 - 6.069

D. Considerations

As the previous genomes the Second Model presented the best results in the experiments. The behavior of the two models showed that both are robust, however, only the Second Model is efficient for SNPS classification. The difference between the sample size of SNPs and the total number of alignments discovered increases the CI for all models of germplasm TSU-1, however, despite that the accuracy of the ORs is still high.

IX. Discussion

The software SNPs MAQ filter has three rules separate, each candidate must meet just one rule, and each rule uses distinct variables. At this point, the network presents a more efficient solution to the classification of mismatches, because it uses all available variables, and as seen, both models are restrictive and informative. The application of the restriction allows the user to reduce the population of SNPs to be studied, conserving the information acquired.

Figure 5 and Figure 6 have the objective to display that the network models maintain the same behavior when applied to a different data set of the data used in training phase. The Second Model presented the best ORs showing more robustness when compared with the First Model.

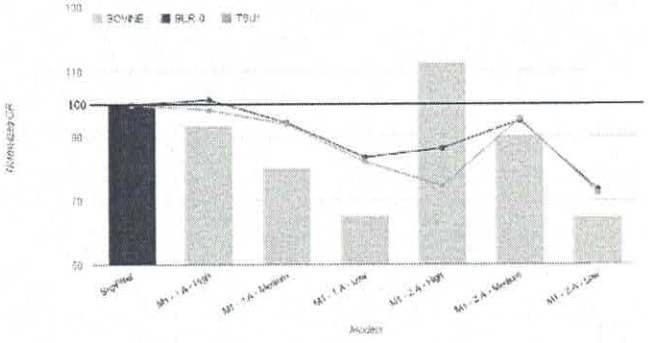

Figure 5: Comparison between normalized OR of First Model.

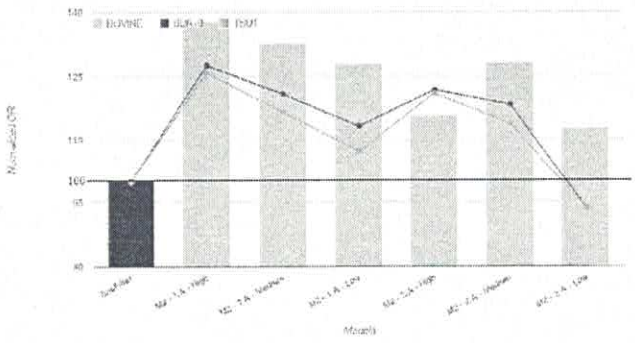

Figure 6: Comparison between normalized OR of Second Model.

X. CONCLUSIONS

The increase in capacity of NGS platforms, which provide data of millions of base pairs in a single run, generates the necessity of constant advances in computational methods for the handling and analysis of this large volume of data aiming a general and greater understanding of the biological species. Among the possible analysis based on genetic material can highlight the research related to SNPs. These surveys can generate relevant knowledge. However, previous steps as the discovery and filtering of these SNPs need to be performed effectively. Specifically for NGS platforms, where reads are short and error-prone, the assembly process is very hard increasing the number of mismatches present in the sample that will be used in the discovery of SNPs step. Any differences in sequencing are a potential SNP in the discovery step. Therefore the necessity of adaptation of computational strategies for the treatment of sequences obtained via NGS.

This work was presented and developed a computational strategy based on computational intelligence and machine learning, with ability to filter SNPs from whole genome (NeuroSNP). In the NeuroSNP building process two different models were examined and compared to the reference filter of MAQ software, namely SNPfilter. In the genomes assessed, NeuroSNP obtained similar or better results than MAQ filter. Computational experiments clearly indicated the potential of the presented learning tool for the detection of SNPs. Their use alone or with traditional filters is presented as an alternative for robust determination of SNPs in different genomes.

Computational experiments clearly indicated the potential of the introduced machine learning tool for SNPs detection when applied in different genomes. The use of a neural network alone or combined with traditional filters presents as an alternative for robust determination of SNPs in different genomes. The adoption of measures like OR showed that the application of the filter augments the chance of finding a positive alignment of SNPs in the sample with the expectation that this new scenario reflects directly in the reduction of false positives.

It is important to notice that the construction of database for training phase of the classifier can be improved mainly in two directions: (i) by defining more specific rules for determining priority of false positives; (ii) using biologically confirmed SNPs for constructing the class of true positives. In any case, the supervised classification tends to enhance its performance with the use of more precise information about the SNPs.

ACKNOWLEDGMENT

The authors thank to reviewers who gave useful comments, and would like to express our gratitude to the National Research Center of Dairy Cattle (Embrapa Dairy Cattle) of Brazilian Agricultural Research Corporation (Embrapa) for providing database and the provision of the necessary infrastructure to conduct this work; to the Graduate Program in Computational Modeling of Federal University of Juiz de Fora (UFJF) for the academic support; and to the Coordination for the Improvement of Higher Level Personnel (CAPES), National Council for Scientific and Technological Development (CNPq) and the State of Minas Gerais Research Support Agency (FAPEMIG) for the financial support for the accomplishment of this paper.

REFERENCES

[1] Bruno Zonovelli, Carlos C. H. Borges, and Wagner A. Arbex. NeuroSNP: Tool to filter SNPs in whole genomic DNA. ICAI, 2014. URL http://www.ucmss.com/cr/main/papersNew/papersAll/ICA3068.pdf.

[2] Heng Li, Jue Ruan, and Richard Durbin. Mapping short dna sequencing reads and calling variants using mapping quality scores. Genome Research, 18(11):1851–1858, 2008. doi: 10.1101/gr.078212.108. URL http://genome.cshlp.org/content/18/11/1851.abstract.

[3] Steffen Nissen. Neural networks made simple. Software 2.0 magazine, (2):14–19, 2005. URL http://fann.sf.net/fann_en.pdf.

[4] Travis C. Glenn. Field guide to next-generation DNA sequencers.Molecular Ecology Resources, 11(5):759–769, September 2011.

[5] Nawar Malhis and Steven J. M. Jones. High quality SNP calling using illumina data at shallow coverage. Bioinformatics, 26(8):1029–1035, April 2010.

[6] Sebastian Eck, Anna Benet-Pagès, Krzysztof Flisikowski, Thomas Meitinger, Ruedi Fries, and Tim Strom. Whole genome sequencing of a single bos taurus animal for single nucleotide polymorphism discovery. Genome Biology, 10(8):R82, 2009. ISSN 1465-6906. doi: 10.1186/gb-2009-10-8-r82. URL http://genomebiology.com/2009/10/8/R82.

[7] Stephan Ossowski, Korbinian Schneeberger, Richard M. Clark, Christa Lanz, Norman Warthmann, and Detlef Weigel. Sequencing of natural strains of arabidopsis thaliana with short reads. Genome Research, 18 (12):2024–2033, 2008. URL http://genome.cshlp.org/content/18/12/2024.abstract.

Sistemas e Tecnologias de Informação

Atas da 10ª Conferência Ibérica de Sistemas e Tecnologias de Informação
Águeda, Portugal
17 a 20 de junho de 2015

Vol. I – Artigos
Tomo 1

Editores
Álvaro Rocha
Arnaldo Martins
Gonçalo Paiva Dias
Luís Paulo Reis
Manuel Pérez Cota

Artigos da Conferência

Artigos dos Workshops

aisti
Associação Ibérica de Sistemas e Tecnologias de Informação

IEEE
PORTUGAL SECTION

universidade de aveiro

Sistemas e Tecnologias de Informação

Atas da 10ª Conferência Ibérica de Sistemas e Tecnologias de Informação
Águeda, Portugal
17 a 20 de Junho de 2015
AISTI | Universidade de Aveiro

Vol. I – Artigos

Tomo 1

Editores
Álvaro Rocha
Arnaldo Martins
Gonçalo Paiva Dias
Luís Paulo Reis
Manuel Pérez Cota

ISBN:
978-898-98434-5-5