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Developing a parsimonius predictor for binary traits in sugar beet (*Beta vulgaris*)

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Abstract Insert your abstract here. Include keywords, PACS and mathematical subject classification numbers as needed.

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1 Introduction

The primary goal of breeding schemes in farm animals and crops is generally to increase the agricultural output. Production traits are typically quantitative continuous variables (e.g. milk yield in dairy cattle, or per hectare yield in maize and rice). Many traits of importance in plant and animal breeding follow nonetheless a discrete categorical distribution, both ordered (e.g. calving ease in cattle, grain texture in rice) and unordered (e.g. grain pigmentation in rice, coat colour in cattle). A special case is that of binomial traits, which can take up only two different values, like disease resistance/susceptibility or presence/absence of a morphological characteristic. Annual bolting (flowering) behaviour and root vigor are examples of binomial traits of agronomic importance in sugar beet (*Beta vulgaris*).

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Advances in biotechnology and genomics, and the advent of high-density molecular markers (especially sinlge-nucleotide polymorphisms, SNP) genotyping have led to the emergence of molecular breeding [18]. One exciting application of molecular breeding is genomic selection: the possibility of predicting the genetic value and future performance of selection candidates solely from their genotypes ([17]). The predictive equations are trained on reference individuals with both genotypic and phenotypic data and then applied to selection candidates with genotypes only. Genomic selection may bring about multiple benefits in breeding programmes such as shorter breeding cycles or more efficient (e.g. traits difficult or expensive to phenotype) and more accurate (e.g. traits with low heritability) estimation of breeding values ([8,11]). Key to the application of genomic selection to breeding programmes are reliable genomic predictions. The recent publication of the reference genome for *Beta vulgaris* genome [4] is facilitating the application of molecular breeding also in this crop species. Pioneering studies on genomic predictions for both continuous ([12,23]) and binary ([2]) traits in sugar beet have already been published.

Genomic predictions are being based on increasing number of molecular markers (e.g. 777K SNP-chip in cattle, 56K SNP-chip in maize, whole-genome sequence data). When a huge number of potential predictors is available, it may be useful to select a subset to limit laboratory and bioinformatics costs, and the time of analysis, while at the same time improving interpretability of results. There is therefore interest in finding the minimum necessary set of information for a specific problem. The principle of parsimony states that a model needs to be simpler than the data it explains (think for instance of K-nearest neighbors -KNN- classifier with K=1), and according to Occam's razor, given two models that explain the data equally well, the simplest has to be chosen ([3]).

The objective of this paper is to present the development of a parsimonious predictor for the binary trait root vigor in a population of sugar beet accessions. SNPs in the panel were ranked based on their relevance and used to classify observations: one SNP at a time was removed, progressively reducing the number of SNPs in the predictive model. We found that it was possible to strongly reduce the dimension of the predictor and still achieve high accuracy.

2 Material and methods

2.1 Plant material and SNP genotypes

The available population comprised 123 individual sugar beet (*B. vulgaris*) plants, 100 with high- and 24 with low-root vigor. Root vigor is related to nutrient uptake from the soil and plant productivity ([22]) and is recorded as a binary trait (either high or low) based on the root elongation rate of eleven-days-old seedlings. No pre-determined root elongation rate threshold was used to classify sugar beets into high or low root vigour. The classification

was subjectively made upon phenotypic inspection and has nevertheless been shown to be robust over time ([22]). The plant material was provided by Lion Seeds Ltd. (UK).

All plants were genotyped for 192 SNP markers with the high-throughput marker array QuantStudio 12K Flex system coupled with Taqman OpenArray technology. Additional details on the genotyping procedure are described in Stevanato et al., 2013 ([21]). After imputation and editing (call-rate $\geq 95\%$, MAF $\leq 2.5\%$) 175 SNPs were left for the analysis. A more detailed description of SNP genotypes and editing procedure can be found in Biscarini et al. ([2]).

2.2 Predictor development procedure

A two-step approach was adopted for the construction of a parsimonious predictor for root vigor in sugar beet. First, the 175 SNP available for the analysis after data editing were ranked based on their relevance for predicting the trait under study. In the second step the set of predictors was progressively reduced by removing the least useful predictors one at a time. At each iteration logistic regression was used to classify observations with the given set of SNPs. As many classification results as the number of SNPs (i.e. 175) were therefore obtained.

2.2.1 Rank of predictors

When many predictors are available -especially if $p > n$- it may be of interest to reduce the dimensionality of the problem by choosing the optimal subset of predictors that best model their relationship with the response variable. A Bayesian model selection method, the binary outcome stochastic search (BOSS) algorithm [20], was applied to identify the best set of predictive SNPs by repeated sampling in a Markov Chain Monte Carlo (MCMC) approach. SNPs were then ranked based on their probability of inclusion in the best predictive model.

In BOSS the relationship between binary observations and predictors is described by a Gaussian latent variable model with a probit link function:

$$P(Y = [0/1]|X) = \phi(X\beta) \tag{1}$$

where $P(Y = [0/1]|X)$ is the probability of having low or high root vigor given the SNP genotyps X, β is a vector of regression coefficients, and ϕ is the normal cumulative distribution function.

The n independent latent variables were normally distributed as $Z_i \sim N(X_i^T\beta, 1)$ (with $i = 1 \ldots n$), and used to model the relationship between SNP genotypes and root vigor:

$$Y_i = \begin{cases} 0 & Z_i \leq 0 \\ 1 & Z_i > 0 \end{cases} \quad \mathbf{Z} = \mathbf{X}\beta + \epsilon \tag{2}$$

BOSS extensively explores the model space to identify relevant predictors, similar to what is done in Best Subset Selection ([10]).

The selection of predictors was performed by introducing a vector of indicator variables $\gamma = (\gamma_1, \ldots, \gamma_p)$ such that $\gamma_i = 0$ if $\beta_i = 0$ and $\gamma_i = 1$ if $\beta_i \neq 0$. A predictor was included in the model if its regression coefficient was not null and the associated indicator variable $\gamma = 1$. The model space to be searched was therefore given by the 2^p possible combinations of SNPs (either included or excluded). This yielded a vector β_γ of size p_γ with only the coefficients for which $\gamma_i = 1$.

The prior for vector γ was chosen from the following beta-binomial (B) distribution:

$$f(\gamma) = \frac{B(p_\gamma + a, p - p_\gamma + b)}{B(a, b)} \tag{3}$$

with parameters a and b related to model size p_γ.

Knowing -from Bayes theorem- that the posterior conditional density for γ is proportional to its prior and the marginal likelihood of $\mathbf{Z}$, the following holds:

$$f(\gamma|\mathbf{Z}) \propto f(\gamma) \cdot f(\mathbf{Z}|\gamma) \tag{4}$$

from which vector γ can be sampled.

The BOSS algorithm is summarised below:

1. initialize the latent variables $\mathbf{Z}$;
2. sample γ through a Metropolis-Hastings sampler from its conditional posterior distribution in equation 4;
3. given $\mathbf{Z}$ and γ, sample β_γ through standard Bayesian linear regression ($\mathbf{Z} = \mathbf{X}_\gamma \beta_\gamma + \epsilon$);
4. given β_γ and $\mathbf{Y}$, sample the vector of latent variables $\mathbf{Z}$ from equation 2;
5. restart from step 2 until $m = 1\,000\,000$ iterations are completed

From the $m = 1\,000\,000$ MCMC iterations the inclusion probabilities for the 175 SNPs were computed and used to rank the predictors. A more detailed description of the BOSS algorithm can be found in Russu et al. ([20]).

2.2.2 Selection of predictors and classification method

SNPs were selected based on the BOSS rank (see section 2.2.1) by progressively removing one SNP at a time. The full set of 175 SNPs was used at first in the prediction model. Subsequently, the m^{th} least relevant SNP (from the BOSS rank) was removed each time, and the resulting $175 - m$ SNPs model was fitted. As a result of this, 175 different predictive models $(175, 174, \ldots, 2, 1$ predictors) were fitted.

With each set of SNP, a logistic regression model for binary outcomes was used to classify observations into low and high root vigor based on the SNP genotypes. The probability of having high root vigor ($P(Y = 1|X) = p(x)$)

was modeled as a linear combination of the predictors (SNPs) through a *logit* link-function in a generalised linear model:

$$logit(p(x_i)) = log\left(\frac{p(x_i)}{1-p(x_i)}\right) = \mu + \sum_{j=1}^{m} z_{ij} SNP_j \quad (5)$$

where $p(x_i)$ is the $P(Y = 1|X)$ for individual i with vector of predictors x_i; SNP_j is the effect of the j_{th} marker; z_{ij} is the genotype of individual i at locus j (0, 1 or 2 for AA, AB and BB genotypes). Equation 5 returns the odds of $p(x)$ which are backtransformed to $P(Y = 1|X)$ through the cumulative distribution function of the logistic distribution (i.e. the logistic function). Individuals with $p(x) > / < 0.5$ were classified as high/low root vigor plants.

Since there were more predictors than observations in model 5 ($p > n$), a ridge logistic regression fitting method [15] was adopted, which consisted in maximizing the following penalized log-likelihood:

$$L(\mu, SNP) = \sum_{i=1}^{n} [y_i log(p_i) + (1 - y_i) log(1 - p_i)] - \frac{1}{2}\lambda \sum_{j=1}^{p} SNP_j^2 \quad (6)$$

where μ is the intercept, SNP is the vector of SNP effects (i.e. the regression coefficients of SNP genotypes) and λ is a tuning parameter that was specified through cross-validation and controls the amount of penalization.

2.2.3 Predictive ability

For each set of SNPs (175 to 1), the predictive ability of the ridge logistic regression model (equation 5) was assessed through a two-fold cross-validation. The 123 samples were randomly split into a training and testing set of approximately equal size. The training set was used to fit the model and estimate SNP effects which were then used to predict root vigor in the testing set. This process was repeated 100 times, each time sampling different training and testing sets. The test error rate in each replicate was computed as:

$$ER_{(n)} = \frac{1}{n} \sum_{i=1}^{n} Err_i \quad (7)$$

where n is the number of observations in the test set and $Err_i = I(y_i \neq \hat{y}_i)$, with $I(\cdot)$ an indicator function which returns a value of 1 if the predicted and observed phenotypes are different, 0 otherwise. The cross-validation error rate was then estimated averaging the test error rate over all $k = 100$ replicates:

$$CV_k = \frac{1}{k} \sum_{i=1}^{k} ER_i \quad (8)$$

The prediction accuracy was then defined as $1 - CV_k$. Besides the total error rate (TER), also the false positive (FPR) and false negative (FNR) rates

were computed. False positives (FP) were defined as true low-root vigor plants predicted as high-root vigor, whereas false negatives (FN) were defined as true high-root vigor plants predicted as low-root vigor. Then, $FPR = {}^{FP}/_{N}$ and $FNR = {}^{FN}/_{P}$, where N and P are the total number of true negative (low-root vigor) and true positive (high-root vigor) samples.

2.3 Comparison with another method to rank predictors

The BOSS algorithm yielded a rank of the SNPs based on their probability of inclusion in the best predictive model. SNPs could be ranked also based on different metrics. For instance, the relative effect on the trait under analysis could be chosen as an indirect measure of the predictive importance of the SNPs. A logistic model of the form $logit(p_i) = \mu + SNP_m$ ($i = 1, \ldots, 123$ plants; $m = 1, \ldots, 175$ SNPs) was fit one SNP at a time in order to estimate marker effects. From estimated marker effects and allele frequencies, the additive genetic variance at each SNP locus was estimated as:

$$V_A = 2pqa^2 \tag{9}$$

where p and q are the frequencies of the two alleles in the population and a is the marker additive effect ([6]). SNPs were then ranked based on decreasing genetic variance and used for predictor selection and classification as in section 2.2.2. Prediction accuracy was estimated as in section 2.2.3.

2.4 Software

Matlab scripts [16] were used to implement the BOSS algorithm for model selection. Classification of observations was done with the Java data mining software *Weka 3* [9]. The open source statistical environment *R* [19] and the open source spreadsheet *Gnumeric 1.12.12* ([7]) were used for data manipulation, the creation of figures and all other statistical analyses.

3 Results

The ranking of SNPs in descending order of predictive relevance from the BOSS algorithm is presented in supplementary table S1. SNPs were ranked based on their probability of inclusion in the best predictive model over 1 000 000 MCMC iterations. The most relevant SNPs were those most often included in the predictive model. The first SNP of the ranking (predictor with the highest probability of inclusion) was *SNP109* on scaffold00456 of chromosome 9: this SNP was therefore included in all 175 SNP subsets (from 175 SNPs to just one single SNP) used for classification. Of the top 20 SNPs, six were on chromosome 9, two each on chromosomes 3, 7 and 8, and one on chromosome 2 of the sugar beet genome. Seven of the top 20 SNPs were not mapped to any

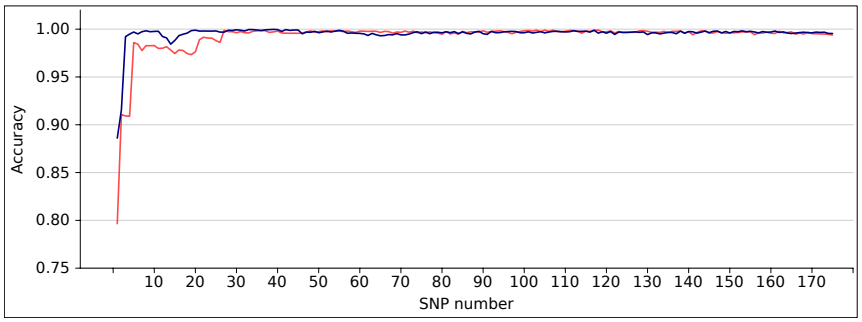

Fig. 1 Accuracy (1 - error rate) of prediction as a function of the number of SNPs included in the classifier: BOSS (blue line) vs logistic regression (red line)

chromosome. The last (least relevant) 20 SNPs were distributed as follows: six on chromosome 4, four on chromosome 1, three on chromosome 7, one on chromosomes 3, 5, 6 and 9; three were unmapped. Chromosome and scaffold information for each SNP in the ranking can be found in the supplementary table S1.

Figure 1 shows the accuracy of prediction (1 - test error) as a function of the number of SNPs used for classification based on both the BOSS (blue line) and SNP-variance (red line) rankings. Prediction accuracy was close to 1 (0.997 or 99.7%) down to approximately 30 SNPs in the classifier. When fewer than 30 SNPs were used to classify observations, the prediction accuracy became less stable, and dropped to a minimum of 0.886 (88.6%) and 0.797 (79.7%) with the BOSS and SNP-variance ranking, respectively. Table 1 reports the total (TER), false positive (FPR) and false negative (FNR) test error rates for all subsets of SNPs (from 175 to 1) used for classification. The average TER over the 175 classifiers was 0.0045 (0.45%) and 0.0075 (0.75%) with the BOSS and SNP-variance rankings. FPR was on average slightly higher than FNR (0.49% vs 0.43% and 0.74% vs 0.73% with the two rankings).

4 Discussion

In this paper a general procedure to reduce the dimension of classification problems has been described. The case of a binary trait (root vigor) in sugar beet (*B. vulgaris*) was chosen as illustration: however, this procedure can in prinicple be extended to any other categorical trait in plants and animals of agricultural interest. In this work, predictors were first ranked for their predictive relevance and then used to assess the predictive performance of progressively smaller classifiers constructed by serially removing each time the least relevant predictor. Alternatively, the two steps could be combined into a single one by using a variable selection method like backward stepwise selection or Bayesian lasso ([10]).

Overall, very few misclassifications were observed for almost every size of the classifier. Starting from about 15-20 SNPs in the model upwards the pre-

diction accuracy stabilized over 99%. Such low error rate is in accordance with previous results published by Biscarini et al. ([2]): these authors found a total error rate of 0.073% using all available SNPs in the classification model for root vigor. Such good predictive ability was related to the high heritability ($h^2 = 0.783$) and oligogenic nature of the trait, and to the linkage disequilibrium (LD) structure among the markers. Also the slightly higher proportion of false positives rather than false negatives is in line with previous results. When using all SNP genotypes for classification, $FPR > FNR$ was found to be likely due -besides unbalanced data- to the population structure (genetic relatedness between high- and low-root vigor lines, [2]). With fewer SNPs, sometimes $FNR > FPR$: this might be related to the specific SNPs used, which may be in stronger or weaker LD with QTLs for root vigor or may lead to different estimates of genetic relationships between sugar beet lines.

4.1 Relative performance of ranking methods

A Bayesian model selection method for binary traits (BOSS) was chosen to rank SNPs by predictive importance for later evaluating increasingly parsimonious predictors. The BOSS ranking was compared to a more intuitive way of ranking SNPs by importance in relation to a specific trait: the proportion of trait variance explained by each SNP. With both SNP rankings the results of classification were very similar: a very high prediction accuracy was observed for most subsets of SNPs included in the model. Only when using few SNPs -$\sim<$ 30- classifications based on the BOSS ranking seem to perform better than the SNP-variance ranking. The classification performance based on the two rankings was compared also by looking at ROC curves ([5]). The two ROC curves overlapped substantially and had both an average AUC (over the 175 SNP subsets) close to 1 (0.997 ± 0.005 vs 0.996 ± 0.012, for the BOSS and SNP-variance rankings).

It may be of interest to look not only at the classification performance of the two rankings but also at the actual rank of the SNP markers when orderd by BOSS inclusion probability or SNP variance. The Spearman correlation between the relative order of each SNP in the two rankings was 0.57. This is a general measure over all 175 SNPs. Figure 2 shows the rank difference between the BOSS and SNP-variance rankings. The top ~ 30 SNPs (the most relevant for prediction) appear to have a stable rank across both rankings. The remaining SNPs have more variable rankings, probably because with $p >\approx 30$ the prediction accuracy is constantly close to 100% and it doesn't make much of a difference which SNP is added to the model. This is confirmed also by the variance of the rank difference (red dotted line in figure 2) which is very low for the top 30 SNPs and increases progressively thereafter.

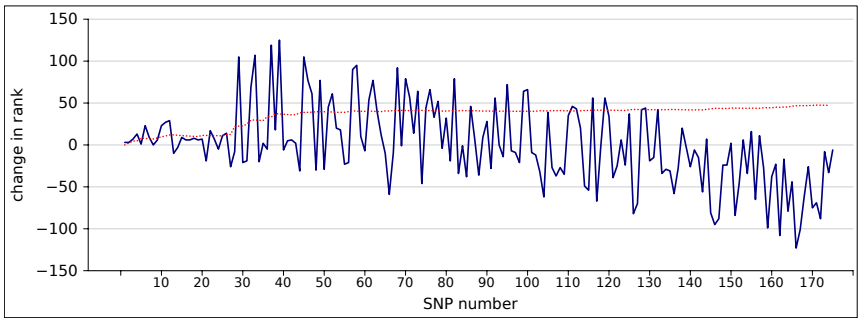

Fig. 2 Comparison of BOSS and logistic regression in terms of relative rank position of relevant SNPs

4.2 Probability of assignment and linkage disequilibrium

Prediction accuracy remained constantly close to one for most sizes of the predictor and began decreasing only for $p <\sim 30$. This was reflected also in the distribution of $P(Y = [0/1]|x)$. The $p_n = (p_1, p_2, \ldots, p_{100})$ percentiles of $P(Y = 1|x)$ from the BOSS ranking are shown in figure 3 (percentiles with values ≥ 0.99 were removed from the plot for the sake of readability -since $TER \sim 0$, $P(Y = 1|x) \sim 1$). The local regression ([13]) fit (blue continuous line) and standard deviation (gray shaded area) of the probability are reported together with the percentiles (black dots). When many SNPs were included in the model, the probabilities of being either high- or low-root vigor were very well separated (clustered at the extremes of the distribution). With fewer SNPs, the probabilities increasingly overlapped, leading to a larger number of misclassifications.

Prediction accuracy increased approximately logarithmically with the number of SNPs, asymptotically approaching 100%. At two SNP densities, though, the prediction accuracy dropped below expectations: between $12 - 18$ and -slightly- $\sim 40 - 60$ SNPs in the classifier (see figure 1 and table 1). The predictive ability of the SNPs may be partly related to the amount of linkage disequilibrium (LD) between them and QTLs relevant for the trait. An indirect estimate of LD between markers and QTLs can be provided by the LD between adjacent markers. This was estimated at each SNP density used for classification. Figure 4) shows the average LD between SNP markers used for classification; the pink shaded areas highlight SNP densities at which prediction accuracy dropped. It is seen that with few SNPs LD between markers is low and estimates are unstable. LD then increases with the number of SNPs, but decreases between $\sim 40 - 70$ SNPs and starts increasing again thereafter. Such LD pattern matches the prediction accuracy curve, suggesting that LD may indeed be related with the ability to correctly classify individuals.

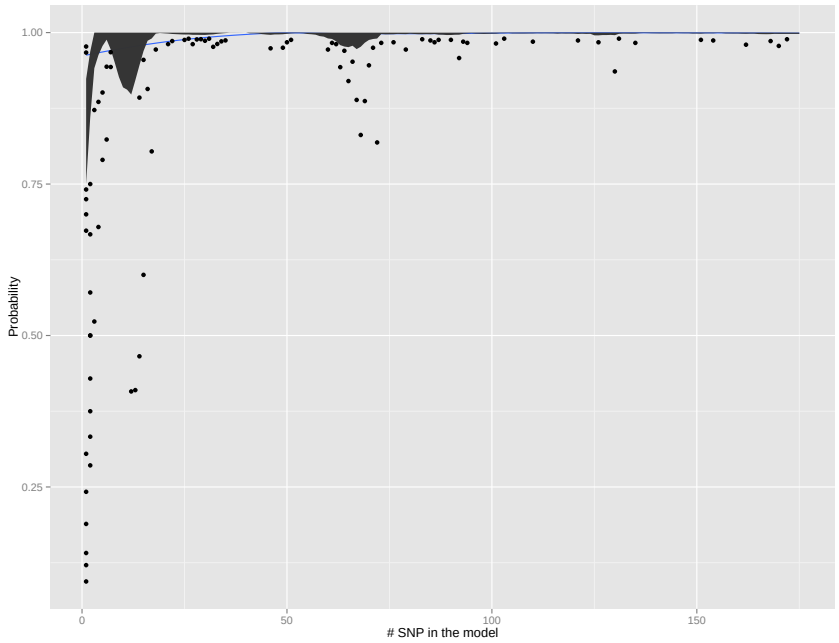

Fig. 3 Distribution of $P(Y = 1|x)$ as a function of the number of SNPs in the classifier: percentiles < 0.99 (black dots), standard deviation (gray shaded area) and LOESS fit (blue line)

4.3 Predictive SNPs

Frequency of important SNPs per chromosome (mention plot: chr 2, 9 and unknown). Variance of SNPs (plots?) peaks on chrom 7 e 9 (+unknown).

Manhattan plot with BOSS weights and weights from the other articles, somehow compared (same chart? two charts? only ten best?).

Do the peaks make sense from the biological perspective? (something on sugar beet genes?)

BOSS probability: 1 big peak + smaller peaks. Compare against SNP density? Maybe the big peak corresponds to a physically isolated SNP, whereas smaller peaks correspond to a cluster of SNPs in LD which individually account for a smaller part of the variation, but together play an important predictive role.

5 Conclusions

This paper showed an approach to the reduction of the dimensionality of predcition problems. A parsimonious predictor has the advantages of being cheaper, easier to handle and of yielding more interpretable results. ...

Fig. 4 Average linkage disequilibrium (LD) for increasing number of SNPs in the predictive model. The pink shaded areas highlight SNP densities for which the prediction accuracy of the classifier dropped

Based on results, a panel of 30-35-40 SNPs is recommended for accurate prediction of root vigor. Already with very few SNPs classification is very accurate, but predictions are more variable in terms of assignment probability and LD between markers and QTLs. (move to breeding applications? Together with development of a custom-chip?)

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Table 1 Total error rate (TER), false positive (FPR) and false negative (FNR) rates as a function of the number of SNPs included in the model, for both the BOSS and SNP variance rankings

	BOSS			SNP Variance		
# SNPs	TER	FPR	FNR	TER	FPR	FNR
1	0.114	0.333	0.061	0.204	0.500	0.132
2	0.085	0.192	0.059	0.089	0.004	0.101
3	0.008	0.033	0.002	0.091	0.005	0.103
4	0.005	0.025	0.001	0.091	0.001	0.113
5	0.003	0.006	0.002	0.014	0.000	0.017
6	0.005	0.011	0.004	0.016	0.001	0.019
7	0.003	0.005	0.002	0.022	0.001	0.028
8	0.002	0.002	0.002	0.017	0.000	0.022
9	0.003	0.000	0.003	0.017	0.000	0.022
10	0.002	0.001	0.003	0.017	0.000	0.021
11	0.002	0.001	0.002	0.020	0.001	0.025
12	0.008	0.001	0.009	0.020	0.002	0.024
13	0.009	0.001	0.011	0.018	0.001	0.023
14	0.016	0.000	0.019	0.022	0.001	0.027
15	0.012	0.000	0.015	0.025	0.003	0.032
16	0.007	0.001	0.008	0.022	0.002	0.027
17	0.005	0.000	0.007	0.022	0.001	0.027
18	0.004	0.001	0.005	0.025	0.002	0.032
19	0.002	0.001	0.002	0.027	0.002	0.033
20	0.001	0.000	0.001	0.022	0.001	0.029
21–30	0.002	0.001	0.002	0.007	0.003	0.008
31–40	0.001	0.000	0.001	0.003	0.002	0.003
41–50	0.004	0.001	0.003	0.004	0.002	0.004
51–60	0.002	0.001	0.004	0.004	0.004	0.003
61–70	0.003	0.001	0.007	0.003	0.003	0.002
71–80	0.004	0.001	0.005	0.003	0.003	0.003
81–90	0.002	0.004	0.002	0.003	0.004	0.003
91–100	0.001	0.002	0.001	0.003	0.005	0.001
101–175	0.001	0.003	0.001	0.002	0.005	0.001

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