

1 *Technical note*

## 2 **Revised calculation of Kalinowski's ancestral and** 3 **new inbreeding coefficients**

4 **Harmen P. Doekes<sup>1,2\*</sup>, Ino Curik<sup>3</sup>, István Nagy<sup>4</sup>, János Farkas<sup>5</sup>, György Kövér<sup>5</sup>, Jack J. Windig<sup>1,2</sup>**

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6 <sup>1</sup> Animal Breeding and Genomics, Wageningen University & Research, P.O. Box 338, 6700 AH, Wageningen,  
7 the Netherlands

8 <sup>2</sup> Centre for Genetic Resources the Netherlands, Wageningen University & Research, P.O. Box 16, 6700 AA,  
9 Wageningen, the Netherlands

10 <sup>3</sup> University of Zagreb, Faculty of Agriculture, Department of Animal Science, Zagreb, Croatia

11 <sup>4</sup> Kaposvár University, Faculty of Agricultural and Environmental Sciences, Kaposvár, Hungary

12 <sup>5</sup> Kaposvár University, Faculty of Economic Science, Kaposvár, Hungary

13 \* Correspondence: harmen.doekes@wur.nl

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15 **Abstract:** To test for the presence of purging in populations, the classical pedigree-based inbreeding  
16 coefficient ( $F$ ) can be decomposed into Kalinowski's ancestral ( $F_{ANC}$ ) and new ( $F_{NEW}$ ) inbreeding  
17 coefficients. The  $F_{ANC}$  and  $F_{NEW}$  can be calculated by a stochastic approach known as gene dropping.  
18 However, the only publicly available algorithm for calculation of  $F_{ANC}$  and  $F_{NEW}$ , implemented in  
19 GRain v2.1 (and in the PEDIG software package), produced biased estimates. The  $F_{ANC}$  was  
20 systematically underestimated and, consequently,  $F_{NEW}$  was overestimated. To illustrate this bias,  
21 we calculated  $F_{ANC}$  and  $F_{NEW}$  by hand for simple example pedigrees. We revised the GRain program  
22 such that it now provides unbiased estimates. Correlations between biased and unbiased estimates  
23 of  $F_{ANC}$  and  $F_{NEW}$ , obtained for example data sets of Hungarian Pannon White rabbits and Dutch  
24 Holstein Friesian cattle, were high ( $> 0.96$ ). Although the magnitude of bias appeared to be small,  
25 results from studies based on biased estimates should be interpreted with caution. The revised  
26 GRain program (v2.2) is now available online and can be used to calculate unbiased estimates of  
27  $F_{ANC}$  and  $F_{NEW}$ .

28 **Keywords:** ancestral inbreeding, new inbreeding, purging, gene dropping, inbreeding depression

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### 30 **1. Introduction**

31 Inbreeding is the mating between (close) relatives and is unavoidable in genetically small  
32 populations. The degree of inbreeding is typically measured with inbreeding coefficients. Individuals  
33 with higher inbreeding coefficients show a lower phenotypic performance on average, a  
34 phenomenon known as inbreeding depression [1-3]. Inbreeding depression occurs because part of  
35 the genetic load in populations, known as inbreeding load, is only expressed in homozygotes [1].  
36 Inbreeding depression is expected to be largely due to partial dominance, i.e. the existence of  
37 (partially) deleterious recessive alleles, although overdominance and epistasis may also play a role  
38 [1, 2, 4].

39 Inbreeding load in a population is not constant, but rather dynamic over time. New deleterious  
40 recessive alleles arise continuously by mutation and these alleles are eroded over time by (natural  
41 and/or artificial) selection and genetic drift [1]. Inbreeding increases the efficiency of selection against  
42 deleterious recessive alleles in a process called purging [1, 5].

43 To test for the existence of purging in populations, various pedigree-based methods have been  
44 proposed [6-8]. Ballou [6] introduced the ancestral inbreeding coefficient, which is the probability  
45 that a random allele in an individual has been previously exposed to inbreeding, i.e. that this allele  
46 has been identical-by-descent (IBD) in at least one ancestor. Kalinowski et al. [7] extended this concept

47 by considering the IBD-status of the individual itself as well. In the Kalinowski approach the total  
 48 pedigree-based inbreeding coefficient is decomposed into an ancestral ( $F_{ANC}$ ) and a new ( $F_{NEW}$ )  
 49 inbreeding coefficient. The  $F_{ANC}$  is the probability that alleles are IBD in the individual while they  
 50 were already IBD in at least one ancestor, while  $F_{NEW}$  is the probability that alleles are IBD for the first  
 51 time in the individual's pedigree [7].

52 To calculate  $F_{ANC}$  and  $F_{NEW}$  (and other inbreeding coefficients), a gene dropping based algorithm  
 53 has been developed and implemented in GRain v2.1 software [9]. The same algorithm has also been  
 54 incorporated in the PEDIG package [10], versions 2007 and later. Various studies have used GRain  
 55 v2.1 [11-15] and PEDIG [16-18] to calculate  $F_{ANC}$  and  $F_{NEW}$ .

56 The objective of this study was to demonstrate that the algorithm in GRain v2.1 (and PEDIG)  
 57 produced biased estimates of  $F_{ANC}$  and  $F_{NEW}$ . For several simple pedigrees, we show how  $F_{ANC}$  and  
 58  $F_{NEW}$  can be calculated by hand. We also investigate the magnitude of the bias for two example data  
 59 sets, one of Hungarian Pannon White rabbits and one of Dutch Holstein Friesian dairy cattle. A  
 60 revised version of the GRain software (v2.2), which provides unbiased calculations of  $F_{ANC}$  and  $F_{NEW}$ ,  
 61 is now available online.

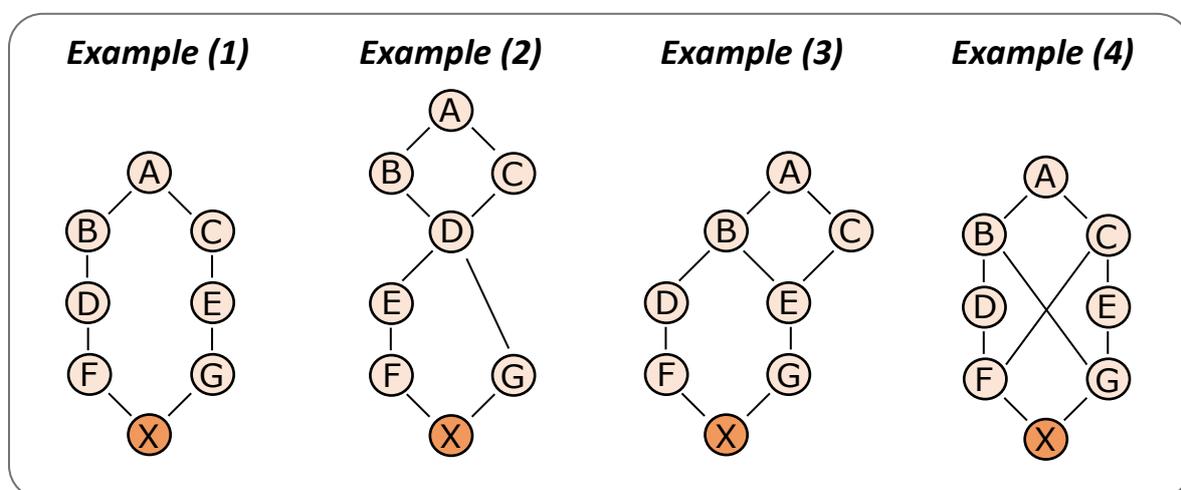
## 62 2. Calculation of ancestral and new inbreeding coefficients by hand

63 For simple pedigrees, Kalinowski's ancestral inbreeding ( $F_{ANC,X}$ ) and new inbreeding ( $F_{NEW,X}$ )  
 64 coefficients of an individual X can be calculated by hand, following Mendelian inheritance principles.  
 65 First, the classical inbreeding coefficient ( $F_X$ ) has to be determined. The  $F_X$  is defined as the probability  
 66 that the two alleles at a random locus in individual X are IBD, and is calculated as [19]:

$$67 \quad F_X = \sum_{i=1}^n (1 + F_i) \left(\frac{1}{2}\right)^{k+1}$$

68 where  $n$  is the number of paths connecting one parent of X with the other parent of X through  
 69 common ancestor  $i$ ,  $F_i$  is the inbreeding coefficient of the  $i^{\text{th}}$  common ancestor, and  $k$  is the number of  
 70 steps in the path. Then,  $F_{ANC,X}$  is calculated as the probability that X is IBD for an allele, given that this  
 71 allele was also IBD in at least one of the ancestors of X. Finally,  $F_{NEW,X}$  can be obtained by subtracting  
 72  $F_{ANC,X}$  from  $F_X$ , since the ancestral and new inbreeding sum up to the total inbreeding.

73 In Figure 1, four example pedigrees are shown. The corresponding inbreeding coefficients are  
 74 provided in Table 1. In example (1), the  $F_X$  equals 0.0078, because it is the inbreeding on ancestor A  
 75 ( $0.5^7$ ). The  $F_{ANC,X}$  for this example is 0, because none of the ancestors of X is inbred. Consequently,  
 76  $F_{NEW,X}$  is equal to  $F_X$  (so 0.0078).



77 **Figure 1.** Example pedigrees for calculation of classical and Kalinowski's inbreeding coefficients.  
 78 Corresponding inbreeding coefficients are shown in Table 1.

79 **Table 1.** Inbreeding coefficients for four example pedigrees (Fig. 1), estimated with revised and previous  
 80 version of GRain.

Pedigree	$F_X$	Revised version (v2.2)		Previous version (v2.1)		Difference in $F_{ANC,X}$
		$F_{ANC,X}$	$F_{NEW,X}$	$F_{ANC,X}$	$F_{NEW,X}$	
(1)	0.0078	0	0.0078	0	0.0078	0
(2)	0.0703	0.0156	0.0547	0.0156	0.0547	0
(3)	0.0390	0.0078	0.0312	0.0039	0.0351	0.0039
(4)	0.1641	0.0390	0.1250	0.0234	0.1406	0.0156

81  $F_X$ : classical inbreeding coefficient of individual X,  $F_{ANC,X}$ : Kalinowski's ancestral inbreeding coefficient of  
 82 individual X,  $F_{NEW,X}$ : Kalinowski's new inbreeding coefficient of individual X.

83 In example (2), the  $F_X$  equals 0.0703, because it is the inbreeding on ancestor D ( $0.5^4$ ) multiplied  
 84 with  $[1 + F_D]$ , where  $F_D$  is the inbreeding coefficient of ancestor D ( $0.5^3$ ). The  $F_{ANC,X}$  is calculated as the  
 85 probability that X is IBD for an allele that was IBD in D as well. Since D is the only inbred ancestor,  
 86 we do not need to consider the IBD status of all other ancestors. The probability that D is IBD for an  
 87 allele from its grandparent A is 0.125 ( $0.5^3$ ). To obtain  $F_{ANC,X}$ , this probability has to be multiplied with  
 88 the probabilities that the allele is transferred to X through both the paths D-E-F-X and D-G-X. The  
 89 probability that E inherits the allele from D is simply 1, because D is IBD. The probability that F  
 90 inherits the allele from E is 0.5 and that X inherits it from F is also 0.5, so the total probability for the  
 91 path D-E-F-X is 0.25 ( $0.5^2$ ). Similarly, the probability for path D-G-X is 0.5. This gives a total  
 92 probability of  $0.125 * 0.25 * 0.5 = 0.0156$  for  $F_{ANC,X}$ . Consequently,  $F_{NEW,X} = F_X - F_{ANC,X} = 0.0703 - 0.0156 =$   
 93  $0.0547$ .

94 In example (3), the  $F_X$  equals 0.0390 and is the sum of inbreeding on ancestor A ( $0.5^7$ ) and ancestor  
 95 B ( $0.5^5$ ). The  $F_{ANC,X}$  is calculated as the probability that X is IBD for an allele that was IBD in ancestor  
 96 E as well. Since ancestor E is the only inbred ancestor, we do not need to consider the IBD status of  
 97 all other ancestors. The probability that E is IBD for an allele from its grandparent A is 0.125 ( $0.5^3$ ).  
 98 This probability has to be multiplied by the probability that this allele is transferred to X through both  
 99 the path E-G-X and B-D-F-X. The probability that G inherits the allele from E is 1, because E is IBD.  
 100 The probability that X inherits the allele from G is 0.5, so the total probability for the path E-G-X is  
 101 0.5. The probability that B carries the allele is 1, otherwise E could not have been IBD. The probability  
 102 that the allele is transferred from B to D, to F and to X is 0.125 ( $0.5^3$ ). This gives a total probability of  
 103  $0.125 * 0.125 * 0.5 = 0.0078$  for  $F_{ANC,X}$ . Consequently,  $F_{NEW,X} = F_X - F_{ANC,X} = 0.0390 - 0.0078 = 0.0312$ .

104 In example (4), the  $F_X$  equals 0.1641 and is the sum of inbreeding on ancestor A ( $0.5^7 + 0.5^5$ ),  
 105 ancestor B ( $0.5^4$ ) and ancestor C ( $0.5^4$ ). The  $F_{ANC,X}$  in this example is the probability that X is IBD for an  
 106 allele that was also IBD in F and/or G (since F and G are inbred ancestors). The  $F_{ANC,X}$  is the sum of  
 107 the probabilities for three scenarios: (i) X is IBD for an allele that was IBD in both F and G, (ii) X is  
 108 IBD for an allele that was IBD in F, but not in G, and (iii) X is IBD for an allele that was IBD in G, but  
 109 not in F. The probability that F is IBD for an allele from A is 0.0625 ( $0.5^4$ ). In that case both B and C  
 110 must be carriers of that same allele and the probability that G is also IBD for the same allele is 0.125  
 111 ( $0.5^3$ ). When F and G are IBD for the same allele, X has to be IBD for that allele as well. Therefore, the  
 112 probability that scenario (i) happens is 0.0078 (i.e.  $0.0625 * 0.125 * 1$ ). If F is IBD for an allele from A,  
 113 the probability that G carries two other "unknown" alleles is 0.375 (i.e.  $0.5 * [1 - 0.5^2]$ ), leaving  $1 - 0.125$   
 114  $- 0.375 = 0.5$  for the probability that G carries one copy of the allele and one copy of an unknown allele  
 115 (scenario ii). In that case the probability that the allele is inherited by X from G is 0.5. The total  
 116 probability for scenario (ii) is thus 0.0156 (i.e.  $0.0625 * 0.5 * 0.5$ ). Because of the symmetry in the  
 117 pedigree, the probability for scenario (iii) is equal to that of scenario (ii), so also 0.0156. Thus, the total  
 118 probability that X is IBD for an allele that was also IBD in F and/or G, i.e. the  $F_{ANC,X}$ , equals  $0.0078 +$   
 119  $0.0156 + 0.0156 = 0.0391$ . Consequently,  $F_{NEW,X} = F_X - F_{ANC,X} = 0.1641 - 0.0391 = 0.1250$ .

### 120 3. Underestimation of ancestral inbreeding by previous version of GRain

121 When  $F_{ANC,X}$  was computed with the previous version of GRain (v2.1), the  $F_{ANC,X}$  for examples  
 122 (1), (2), (3) and (4) from Figure 1 equaled 0, 0.0156, 0.0039 and 0.0234, respectively (Table 1). Although  
 123 the coefficients for examples (1) and (2) were correct, the  $F_{ANC,X}$  coefficients for examples (3) and (4)  
 124 were underestimated. Note that example (3) is equivalent to the example used by McParland et al.  
 125 [17], Figure 1a in their paper, for which they reported the incorrect  $F_{ANC,X}$  estimate of 0.0039.

126 The underestimation of  $F_{ANC,X}$  was caused by a sometimes incorrect tracking of IBD-status of  
 127 ancestors throughout the pedigree. In the previous version of GRain (v2.1), each individual was given  
 128 a flag that indicated whether one of the individual's ancestors had been IBD (1 if true, 0 if false). This  
 129 flag was calculated as the sum of the flags of the parents, divided by two. Thus, when both parents  
 130 had a flag of 1, the flag of the offspring would also be 1, which is correct. However, when only one  
 131 of the parents had a flag of 1 (and the other 0), the offspring would get a value of 0.5, which is  
 132 incorrect. In the revised version of GRain (v2.2), this issue was solved by obtaining the flag of an  
 133 offspring as the maximum of the flags of its parents.

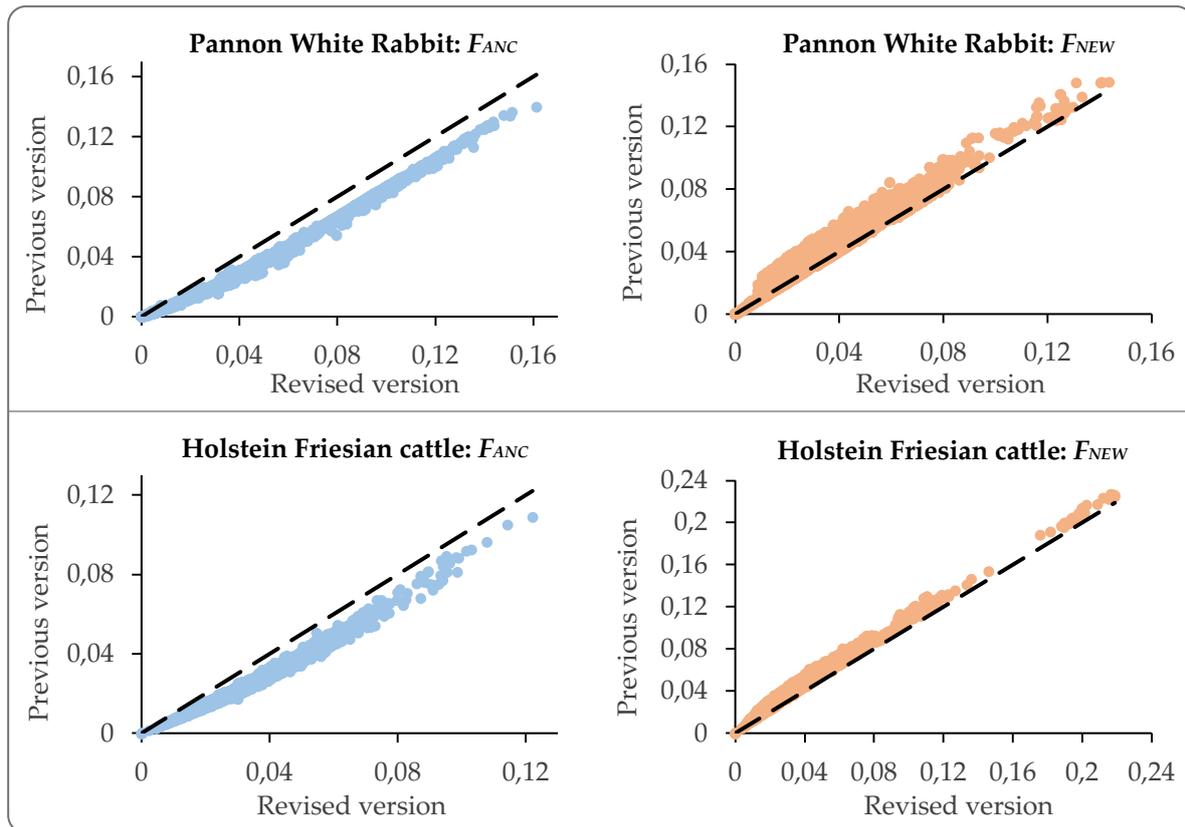
134 To clarify, in example (2) in Figure 1, whenever ancestor D was IBD, both parents F and G had  
 135 a flag of 1 and X also got a flag of 1. Therefore, the  $F_{ANC,X}$  was estimated correctly. In example (3),  
 136 however, whenever ancestor E was IBD, parent G had a flag of 1 and parent F had a flag of 0 and, as  
 137 a result, X got a flag of 0.5. Therefore, the  $F_{ANC,X}$  for example (3) was underestimated by exactly a  
 138 factor two. In example (4), whenever both F and G were IBD, X got a flag of 1. This happened in  
 139 0.0078 of the simulations (see explanation in the previous section for calculation by hand, scenario  
 140 (i)). When only parent F or parent G was IBD, while the other parent was not, X got a flag of 0.5. This  
 141 happened in  $0.0156 + 0.0156 = 0.0312$  of the simulations (see explanation in the previous section for  
 142 calculation by hand, scenarios (ii) and (iii)). Therefore, the  $F_{ANC,X}$  for example (4) was underestimated  
 143 by a factor between one and two. More precisely, the underestimated  $F_{ANC,X}$  was equal to  $0.0078 + (0.5$   
 144  $* 0.0312) = 0.0234$ .

### 145 4. Examples for Pannon White Rabbits and Holstein-Friesian cattle

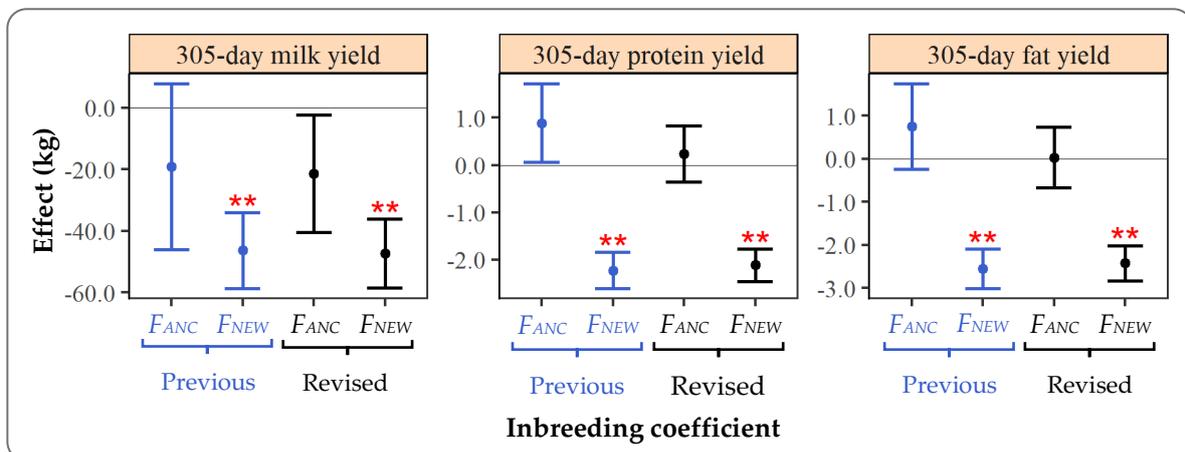
146 To investigate the impact of the incorrect estimation, we computed  $F_{ANC}$  and  $F_{NEW}$  for two  
 147 example data sets, using both the previous and revised version of GRain, and  $10^6$  replications. The  
 148 first data set was a pedigree of 22,781 rabbits of the Hungarian Pannon White (PW) breed. The second  
 149 data set contained 37,061 Dutch Holstein-Friesian (HF) cows, which were part of a larger pedigree of  
 150 167,924 individuals and were used by Doekes et al. [20] to investigate the effects of ancestral and new  
 151 inbreeding on various traits in HF cattle.

152 For both the PW and HF data set, the total inbreeding coefficients ( $F$ ) were identical between the  
 153 previous and revised version of GRain (v2.1 versus v2.2). The  $F_{ANC}$  in the previous version, however,  
 154 was generally underestimated and the  $F_{NEW}$  was overestimated (Figure 2). For the PW data set and  
 155 for inbreeding coefficients above zero, the  $F_{ANC}$  from the previous version was on average 0.65 times  
 156 the revised  $F_{ANC}$  (and the  $F_{NEW}$  was 1.27 times the revised  $F_{NEW}$ ). For the HF data set and inbreeding  
 157 coefficients above zero, the  $F_{ANC}$  from the previous version was on average 0.71 times the revised  $F_{ANC}$   
 158 (and the  $F_{NEW}$  was 1.36 times the revised  $F_{NEW}$ ). Pearson correlation coefficients between coefficients  
 159 estimated with the previous and revised version were high. For the PW data set, the correlations  
 160 between the previous and revised version equaled 0.997 and 0.968 for  $F_{ANC}$  and  $F_{NEW}$ , respectively. For  
 161 the HF data set, these correlations equaled 0.993 and 0.987, respectively. This indicates that the  
 162 underestimation of  $F_{ANC}$  (and overestimation of  $F_{NEW}$ ) did not strongly affect the ranking of animals.

163 For the Holstein-Friesian data set, we also investigated potential differences in inbreeding  
 164 depression estimates for  $F_{ANC}$  and  $F_{NEW}$  calculated with the previous and revised version of GRain. In  
 165 general, differences were rather small (Figure 3). For example, the effects of  $F_{ANC}$  on 305-day milk  
 166 yield were -19.1 kg for the previous version and -21.4 kg for the revised version. Standard errors for  
 167 the inbreeding depression effects were smaller when the revised version of GRain was used to  
 168 estimate  $F_{ANC}$  and  $F_{NEW}$  than when the previous version was used. The overall conclusion that new  
 169 inbreeding is more harmful than ancestral inbreeding, however, was the same for both versions.



170 **Figure 2.** Relationship between Kalinowski’s inbreeding coefficients calculated with previous (v2.1) and revised  
 171 (v2.2) version of Grain, for two example data sets of Pannon White rabbits (n = 22,781) and Holstein Friesian  
 172 cattle (n = 37,061). The dashed line indicates  $y = x$ , i.e. a relationship in which there is no difference in the  
 173 estimation.  $F_{ANC}$ : Kalinowski’s ancestral inbreeding coefficient.  $F_{NEW}$ : Kalinowski’s new inbreeding coefficient.



174 **Figure 3.** Effect of a 0.01 increase in Kalinowski’s ancestral ( $F_{ANC}$ ) and new ( $F_{NEW}$ ) inbreeding on yield traits in  
 175 Dutch Holstein Friesian cattle (n = 37,061), for  $F_{ANC}$  and  $F_{NEW}$  calculated with the previous (v2.1) and revised  
 176 (v2.2) version of GRain. The same model was used as in Doekes et al. [20].

## 177 5. Conclusions

178 The previous version of GRain software (v2.1) systematically underestimated Kalinowski’s  
 179 ancestral inbreeding and, consequently, overestimated Kalinowski’s new inbreeding coefficients.  
 180 Although the magnitude of bias was rather small, results from studies based on biased estimates  
 181 should be interpreted with caution. The GRain software has been revised and the revised version  
 182 (v2.2), which provides unbiased estimates of Kalinowski’s inbreeding coefficients, can be  
 183 downloaded from <https://boku.ac.at/nas/nuwi/software/>.

184 **Author Contributions:** HD and JW performed the Holstein Friesian data analysis; JF and GK performed the  
 185 Pannon White data analysis; HD prepared the manuscript. HD, IC, IN, JF, GK and JW participated in the  
 186 interpretation of results and revision of the manuscript. All authors have read and agreed to the published  
 187 version of the manuscript.

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