

**GROWTH CURVE AND BODY WEIGHT IN GOETTINGEN MINIPIGS**  
**A PHENOTYPIC AND GENETIC STUDY**

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**“I am very proud to be called a pig.  
It stands for pride, integrity and guts.”**

Ronald Reagan (1911-2004)

## **Preface**

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## Zusammenfassung

Die vorliegende Arbeit befasst sich mit der Untersuchung einer möglichen Gewichtsreduzierung beim Göttinger Minischwein und der Ermittlung einer bestmöglichen Selektionsstrategie für dieses Merkmal. Die Ziele waren die Analyse der Körpergewichtsentwicklung des Göttinger Minischweins und die Schätzung genetischer Parameter für Körpergewicht. Weiterhin wurden verschiedene Selektionsstrategien untersucht, um anschließend ein neues Zuchtschema aufstellen zu können.

In einem ersten Schritt wurde das Wachstum der Minischweine untersucht. Die Gewichtsentwicklung der Minischweine wurde durch Modellierung von Wachstumskurven mit verschiedenen nicht-linearen und linearen Wachstumsfunktionen analysiert und mit der Gewichtsentwicklung von Mastschweinen verglichen. Dazu wurden Gewichtsdaten der zwei dänischen Populationen benutzt. Insgesamt wurden 189'725 Gewichte von 33'704 Tieren, die in einem Altersabschnitt von der Geburt (Tag 0) bis zum 700. Lebenstag erfasst wurden, für die Untersuchung herangezogen.

Die verschiedenen Wachstumsmodelle wurden mit dem Informationskriterium von Akaike (AIC) miteinander verglichen, wobei niedrige Werte eine gute Anpassung bedeuten. Die gesamte Wachstumskurve der beiden Populationen betrachtend, ergaben sich die niedrigsten AIC Werte für die Polynome 3. und 4. Ordnung. Unter den nicht-linearen ergab die Logistische Funktion den höchsten AIC Wert und weist somit die schlechteste Anpassung für die verwendeten Gewichtsdaten auf.

Ein Vergleich mit Mastschweinen zeigte, dass Minischweine eine annähernd lineare Gewichtsentwicklung im Alter von 0 bis 160 Tagen aufweisen. Mastschweine hingegen zeigen sehr geringe tägliche Zunahmen im ersten Drittel der untersuchten Zeitperiode in Relation zu einem spezifischen Endgewicht. Später haben Mastschweine erhöhte tägliche Zunahmen was in einer mehr sigmoiden Wachstumskurve resultiert.

Nach der Analyse der Gewichtsentwicklung des Göttinger Minischweins wurden genetische Parameter für das Gewicht geschätzt, um das Potential für eine Zucht auf niedriges Körpergewicht zu untersuchen. In einer ersten Studie wurden genetische Parameter für den Altersabschnitt von 30 bis 400 Tagen mit einem Random Regression Modell (RRM) geschätzt. Das RRM beinhaltet den zufälligen Effekt des Tieres, der permanenten Umwelt und der Wurfumwelt. Regressionen der zufälligen Effekte wurden mit dem Legendre

Polynom 2. Ordnung modelliert. Acht verschiedene Altersklassen wurden gebildet, um heterogene Restvarianzen berücksichtigen zu können.

Die Heritabilitäten waren moderat und lagen in einem Bereich von 0,21 (375 Tage) bis 0,25 (275 Tage). Genetische und phänotypische Korrelationen zwischen den Gewichten in unterschiedlichen Altersklassen nahmen mit zunehmender zeitlicher Distanz zwischen den Wiegunen ab, ein Umstand, auf den bei der Bildung eines neuen Zuchtschemas besondere Rücksicht genommen werden muss. Die Analyse der Eigenfunktionen zeigte, dass Selektion auf niedriges Körpergewicht über den gesamten untersuchten Zeitabschnitt positive Effekte auf dieses Merkmal hat.

Um detaillierte Aussagen treffen zu können und mit einem Fokus auf die Praktikabilität, wurden genetische Parameter für einen Altersabschnitt von 30 bis 700 Tagen geschätzt, um auch einen Überblick im höheren Alter zu haben. Zusätzlich wurden die Parameter mit einem Mehrmerkmalsmodell und einem Random Regression Modell geschätzt, um das geeignete Modell für eine routinemäßig ablaufende Zuchtwertschätzung zu ermitteln. Ein weiteres Ziel dieser Studie war das Auffinden der besten Selektionsstrategie für die Zucht auf ein genetisch kleineres Minischwein. Dafür wurden 19'505 Gewichte von 3'461 Minischweinen analysiert.

Die Heritabilitäten waren moderat, wobei die Werte des RRM etwas höher waren. Genetische Korrelationen zwischen Gewichten an unterschiedlichen Tagen nahmen mit zunehmender zeitlicher Distanz zwischen den Messungen ab, was bereits für den Altersabschnitt 30 bis 400 Tage gezeigt wurde.

Ein Zuchtziel für die *Relative Gewichtsreduzierung (RGR)* wurde geschaffen, in welchem die Gewichtsreduzierung innerhalb Altersklasse in Prozent des aktuellen Körpergewichts ausgedrückt wird. Die RGR ist gewichtet in Abhängigkeit von dem Anteil der verkauften Tiere von einer Altersklasse zur nächsten. Der erwartete Zuchtfortschritt wurde für zwei verschiedene Selektionszeitpunkte (80 und 150 Tage) berechnet, wobei die Selektion am 150. Tag zu einem höheren Zuchtfortschritt im Merkmal *RGR* geführt hat.

Weiterhin wurden in dieser Arbeit verschiedene die Selektion betreffende Aspekte, wie z.B. der Verlust an genetischer Varianz, markergestützte Selektion und Inzuchtdepression, diskutiert.



## Summary

The main focus of this thesis was the examination of a possible body weight reduction in Goettingen minipigs and the detection of an optimal selection strategy for this trait. The aims were the analysis of body weight development of the Goettingen minipig and the estimation of genetic parameters for body weight. Further, different selection strategies had to be examined to build up a new breeding scheme.

As a first step, the growth pattern of the Goettingen minipig was studied. The body weight development of minipigs was investigated by modeling growth curves with different non-linear and linear functions and by comparing their body weight development with the development of normal fattening pigs. Data of two Danish sub-populations were used. In total 189,725 body weight measurements of 33,704 animals collected from birth (d 0) to 700 d of age were analyzed.

The different growth models were compared by using the Akaike's Information Criterion (AIC), whereas a small AIC value indicated a good fit. Regarding the whole growth curve linear polynomials of third and fourth order of fit had the smallest AIC values for the two sub-populations. Among the nonlinear functions the Logistic had the highest AIC value indicating the poorest fit.

A comparison with fattening pigs showed that the minipigs have a nearly linear body weight development in the time period from birth to 160 d. Fattening pigs have very low weight gains in the first third of the examined time period in relation to a specific end weight. Later fattening pigs have increasing daily weight gains resulting in a growth curve that is more s-shaped than the growth curve of the minipig.

After analyzing the body weight development of minipigs, genetic parameters for body weight were estimated to discover the potential for breeding on low body weight. In a first study, genetic parameters were estimated for a time period of 30 to 400 days with a random regression model (RRM). The RRM included random animal, common litter environment and permanent environment effects, respectively. Regressions for the random effects in the RRM were modeled using Legendre polynomials of second of fit. Eight age classes were built to consider heterogeneous residual variances.

The heritabilities were moderate and ranged from 0.21 (375 d of age) to 0.25 (275 d of age). Genetic and phenotypic correlations between body weights in different age classes decreased with increasing distance between age classes, a circumstance which has to be

focused on when building up a new breeding scheme. The analysis of eigenfunctions showed that a selection for low body weight has positive effects on this trait throughout the whole range of time.

To get more into detail and with a focus on practicability genetic parameters were estimated for a time period of 30 to 700 days to have an overview also over later ages. Further, the parameters were estimated using a multiple trait model (MTM) and a random regression model (RRM) to detect which model is more appropriate for routinely working breeding value estimation. Another aim was to find out the best selection strategy to get a genetically smaller minipig in the future. Therefore, 19,505 body weight measurements of 3,461 Goettingen minipigs were analyzed.

Heritabilities were moderate with slightly higher values estimated with the RRM. Genetic correlations between body weight measurements at different ages were decreasing with increasing time lag between the measurements as it was already shown for the time period of 30 to 400 days.

An operational breeding goal for relative weight reduction (*RWR*) was suggested in which the weight reduction in each age class is expressed as per cent of the actual body weight and is weighted according to the proportion of animals sold in this age class. Expected genetic progress was calculated for two different selection ages (80 and 150 d), whereas the selection at 150 d of age resulted in a higher genetic progress for *RWR*.

Further, several aspects related to selection like decrease of genetic variance, marker-assisted selection or inbreeding depression were discussed in this thesis.

## **1<sup>st</sup> CHAPTER**

### **General introduction**

## General introduction

Since centuries the pig is not only known as a meat producing animal but also as an animal model for research in human medicine. Due to the influence of the Catholic Church in the High Middle Ages it was not allowed to dissect human bodies for medical research. But already that time people knew about the high similarities between humans and pigs and used pigs to investigate human diseases. Also the first book about anatomy of animals, which was written 1120 AD, is about the anatomy of pigs (Driesch and Peters, 2003).

Nowadays, pigs are widely used as laboratory animals for biomedical research. The number of used laboratory pigs increased in Germany from 1995 to 2005 from 9,500 to 14,000. However, compared to mice, which had the highest percentage in 2005 with 59 % of all used laboratory animals in Germany, pigs still have a low percentage of only 0.6 % (BMELV, 2006). Svendsen (2006) gives a number of about 60,000 pigs which are used per year for scientific research in the EU. Among pigs, miniature breeds were developed for the special demands which occur in experiments. Their body weight is much lower than that of normal pig breeds and as a consequence the costs for experiments are reduced when the test compounds are dosed per kg body weight of the recipient. A further reduction of body weight in the future could therefore be of considerable economical advantage for the research facilities.

The development of a new approved drug costs about 800 Mio. US \$, that is 250 % more than 10 years ago (DiMasi et al., 2003). Preclinical tests, in which animal experiments are included, amount ca. 40 % of the total costs, whereas the proportion between preclinical and clinical tests changed so that the costs for preclinical tests are now relatively lower than for clinical studies. Even though researchers are anxious to reduce animal experiments as much as possible, these experiments are still essential to assess the effect of new drugs or techniques in the context of the whole metabolism which cannot be simulated or assessed through in vitro techniques like cell cultures. All animal experiments are underlying strict laws and official controls. In drug development, animal models are mainly used for the assessment of effectivity, pharmacokinetic studies, dosing and toxicology.

The minipig became more and more popular as a laboratory animal in the last years because of its high anatomical and physiological similarities to humans (Brandt et al., 1997). The main similarity between humans and minipigs which is attracting researchers is

the skin. The minipig epidermis has more or less the same thickness as the human epidermis. Also the cardiovascular, the intestinal and the immune system are more similar between pigs and humans than between humans and other non-rodent experimental animals like dogs or primates (McAnulty, 1999).

For toxicological studies one rodent and one non-rodent animal model has to be used. Mice and rats are the mostly used rodents, whereas rabbits are widely used as non-rodent animal model. An overview over all used laboratory animals in Germany is given in Table 1 for the year 2005. In this table, minipigs are included in the 14,004 pigs. Of all minipigs, around 1,000 Goettingen minipigs were sold to Germany in 2005 (Ellegaard Goettingen minipigs, ApS, Denmark, personal communication).

Prices of minipigs are in the same range than prices of dogs but they are much cheaper than primates. Ethical problems are much less with pigs than with primates or dogs due to the fact, that they are not caught for the special purpose of testing medical drugs or techniques as it is done with wild-living primates and that they are not kept as companions of humans like dogs (Gad, 2007).

The most important minipig breeds which are used in medical research are among others the Goettingen minipig, the Minnesota minipig, the Yucatan minipig and the Hanford minipig. Even though the Minnesota minipig was developed quite early in 1949 (Dettmers et al., 1965), the Goettingen minipig, developed in 1960's at the University of Goettingen, Germany, is today the main minipig breed used in medical experiments. It combines the low weight and slim body shape of the Minnesota minipig, the high fertility of Vietnamese potbellied pigs and the white skin of German Landrace pigs (Glodek and Oldigs, 1981). Besides the base population in Germany, Goettingen minipigs are bred in two populations in Denmark since 1992 and one population in the USA since 2002 in full-barrier breeding facilities to provide laboratory animals with the highest hygienic standard.

The breeding system for Goettingen minipigs differs considerably from breeding systems for meat producing pigs. Breeders of fattening pigs aim an optimization of the discounted net profit, which means to have maximum profit in the important traits like average daily gain, leanness and fast growth produced with minimum costs (Olsen and Sehested, 2000).

**Table 1.** Number of the different laboratory animals used in Germany in 2005, the percentage of each species in each group and over all groups

Group	Species	n	% in each group	% over all groups
Rodents	Mice ( <i>Mus musculus</i> )	1,432,492	69.5	
	Rats ( <i>Rattus norvegicus dom.</i> )	571,257	27.7	
	Guinea pigs ( <i>Cavia aperea</i> )	40,297	2.0	
	Hamster ( <i>Mesocricetus auratus</i> )	8,581	0.4	
	Other rodents	7,919	0.4	
	<b>Total</b>	<b>2,060,546</b>	<b>100.0</b>	<b>85.4</b>
Non-rodent mammals (without rabbits)	Rabbits ( <i>Oryctolagus cuniculus</i> )	105,293		4.4
	Cats ( <i>Felis catus</i> )	1,023	3.7	
	Dogs ( <i>Canis lupus familiaris</i> )	4,982	18.0	
	Ferrets ( <i>Mustela putorius furo</i> )	560	2.0	
	Other Canines	235	0.8	
	Horses, donkeys etc.	755	2.7	
	Pigs ( <i>Sus scrofa</i> )	14,004	50.5	
	Goats ( <i>Capra hircus</i> )	283	1.0	
	Sheep ( <i>Ovis gmelini aries</i> )	3,652	13.2	
	Primates	2,105	7.6	
	Other mammals	123	0.5	
	<b>Total</b>	<b>27,722</b>	<b>100.0</b>	<b>1.2</b>
Other vertebrates	Quails ( <i>Coturnix coturnix</i> )	4,159		0.2
	Birds	93,858		3.9
	Reptiles	153		0.01
	Amphibians	16,577		0.7
	Fishes	101,551		4.2
<b>Total</b>		<b>2,412,678</b>		<b>100.0</b>

In contrast, Goettingen minipigs, which are under breeding control of the University of Goettingen, are bred considering the demands of the customers, i.e. the researchers conducting biomedical studies. Besides a preferably high uniformity in the pigs, e.g. concerning body weight at a certain age, skin and eye color, they should be as small as possible, show a calm temperament, reduced hair coat, useful ear veins and no abnormalities. Another specialty in Goettingen minipigs compared to normal pig breeds is

that they are not sold at a certain weight or age but they are available for the customers at all ages. This is due to the fact that all studies differ in their aims and minipigs of different ages are needed for different purposes. Most of the minipigs are used for toxicology test with an age of 3 to 6 months.

Since the development of the breed, Goettingen minipigs were phenotypically selected for *low body weight* on the basis of birth and weaning weight (Glodek and Oldigs, 1981). Since the 1970's the breeding goal focused more on the trait *litter size* to improve the breeding performance of sows because of a high demand for Goettingen minipigs. This resulted in a positive development of body weight due to a slightly positive correlation between the traits *litter size* and *body weight* (Ferguson et al., 1985). At the moment, breeding values are only estimated for the trait *number of piglets born alive* to select animals with a high breeding performance on a genetic basis. But due to an increasing need of Goettingen minipigs in medical research, it is more and more important to consider the customers' demand of a lighter and smaller minipig. Therefore it is necessary to include the trait *low body weight* in the breeding goal and to select for it on the basis of breeding values.

The aims of this study were firstly the investigation of minipig growth in chapter 2 which included the detection of the best model for fitting minipig growth and the comparison of weight development of minipigs and fattening pigs to emphasize the differences in body weight development of these two breeds. Further, genetic parameters for body weight were estimated in chapter 3 using different data sets and models for analyzing the genetic background of this trait. Finally, in chapter 4 a new breeding scheme was developed to improve the weight reduction in the future considering different selection strategies.

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## **2<sup>nd</sup> CHAPTER**

### **Modeling the growth of the Goettingen minipig**

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## Modeling the growth of the Goettingen minipig

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### Abstract

The Goettingen minipig developed at the University of Goettingen, Germany, is a special breed for medical research. As a laboratory animal it has to be as small and light as possible to facilitate the handling during experiments. For achieving the breeding goal ‘small body size’ in the future, the growth pattern of the minipig was studied. This study deals with the analysis of minipig body weight development by modeling growth curves with different non-linear and linear functions and the comparison to the body weight development of normal fattening pigs. Data were provided by Ellegaard Goettingen minipigs, Denmark, where two sub-populations of the Goettingen basis population are housed. In total 189,725 body weight recordings of 33,704 animals collected from birth (d 0) to 700 d of age were analyzed. Seven different non-linear growth functions and four different polynomial functions were applied. The different growth models were compared by using the Akaike’s Information Criterion (AIC). Regarding the whole growth curve linear polynomials of third and fourth order of fit had the smallest AIC values indicating the best fit for the used minipig body weight data. Among the nonlinear functions the Logistic had the highest AIC value. A comparison with fattening pigs showed that the minipigs have a nearly linear body weight development in the time period from birth to 160 d. Fattening pigs have very low weight gains in their first 7 weeks in relation to a specific end weight. After 7 weeks fattening pigs have an increasing body weight development resulting in a growth curve that is more s-shaped than the growth curve of the minipig. Based on these results further studies can be conducted to analyze the growth with random regression models and to estimate variance components for optimizing the strategies in minipig breeding.

### Keywords

Body weight development, growth curve, growth model, Goettingen minipig

## Introduction

The Goettingen minipig is an important laboratory animal, especially used for the safety assessment of new pharmaceuticals and for surgery purposes and disease models, because of shared anatomic and physiologic characteristics with humans (Brandt et al., 1997). The breed was developed in the 1960s at the University of Goettingen, Germany. After 30 years of successful breeding with a focus on breeding goals like small body size, unpigmented skin and adequate fertility, 38 pregnant sows were brought to the Ellegaard farm in Denmark in 1992 to build up a new population. Today there are about 3,500 Ellegaard Goettingen minipigs under breeding control of the University of Goettingen.

The main difference between a minipig and a normal sized pig is the smaller body size of the minipig. Goettingen minipigs should have a mature body weight of 35 to 45 kg (Bollen et al., 1998). This small body size is advantageous for the reduction of rearing and breeding costs and for a comfortable handling of the minipigs during medical research. It can also be assumed that not only the mature body weight of minipigs differs from fattening pigs but also the characteristics of body weight development as far as the fattening pigs have been selected for fast growth in the last two-thirds of the fattening period. In comparison to fattening pigs the growth of minipigs should be slow, mainly in the first months after birth so that the minipigs have a low body weight when entering laboratory facilities with an average age of 3 to 6 months.

Knowing the growth pattern of minipigs is necessary for later genetic research that will be conducted on this issue, e.g., estimation of variance components for growth at a certain age. The aims of this study were the application of different non-linear and polynomial functions to describe the body weight data of minipigs and the investigation of the difference in body weight development to fattening pigs. Results are prerequisites for the application of random regression models for estimating genetic parameters.

## Data and Methods

### *Growth Curves Modeled over all Data*

**Data Description.** For the analysis of growth, the data were provided from Ellegaard Goettingen minipigs with a total number of 199,764 body weight records of 33,749 animals acquired from 1995 to 2005. In this time period there was no organized selection

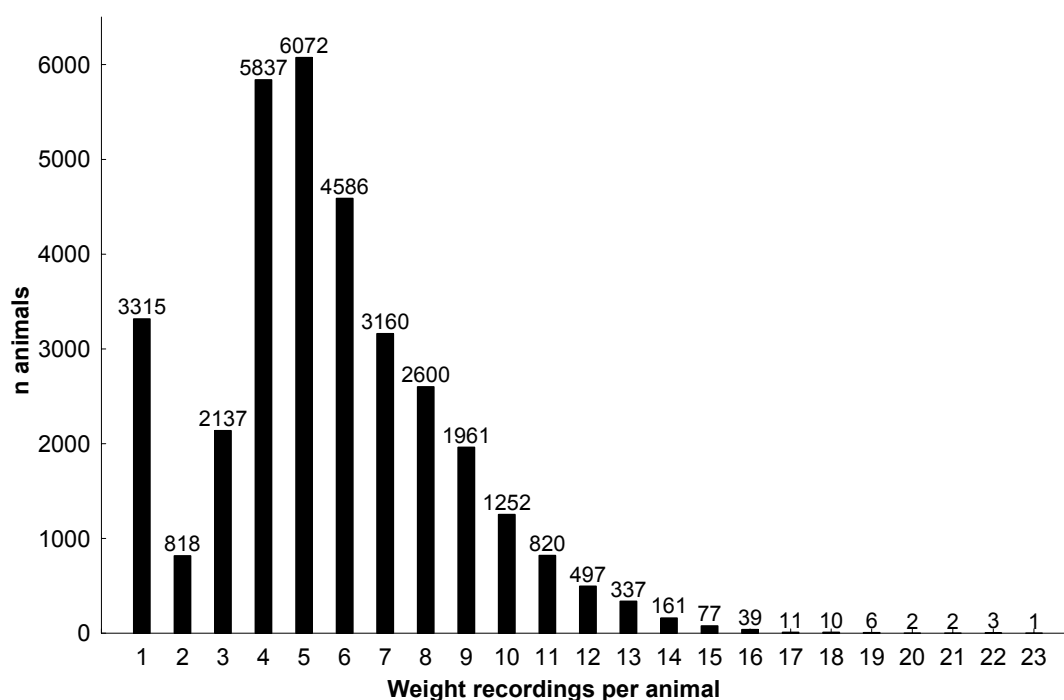
for body weight. Minipigs were selected for breeding because of low inbreeding coefficients and adequate exterior traits like white skin and little hair coat. Due to scarcity, body weight data measured after 700 d of age were excluded from the analyses. Outliers of the data set were detected using the influence diagnostics as recommended by Belsley et al. (1980). With this method the influence of each observation on the estimates is measured. Influential observations are those that appear to have a large influence on the parameter estimates. The method of Belsley et al. (1980) is incorporated in the SAS procedure REG by using the INFLUENCE option in the MODEL statement. The studentized residual was used for analyzing the influence of each weight record. The studentized residual was calculated as follows:

$$RSTUDENT = \frac{r_i}{s_{(i)}\sqrt{(1-h_i)}}$$

where  $r_i = y_i - \hat{y}_i$ ,  $s_{(i)}^2$  is the error variance estimated without the  $i$ th observation and  $h_i$  is the hat matrix, which is the  $i$ th diagonal of the projection matrix for the predictor space. Belsley et al. (1980) suggest paying special attention to all observations with RSTUDENT larger than an absolute value of 2. We discarded all records lying outside the 95 %-confidence interval [-1.99; 2.15]. This resulted in a total number of 189,725 body weight records of 33,704 animals that were used for the growth analysis.

The minipigs were weighed routinely without a special treatment like starvation before weighing. The animals were weighed routinely at various intervals. On average there have been 5.63 body weight recordings per minipig with a maximum number of 23 body weight recordings (Figure 1). Nearly all animals were weighed on their day of birth (d 0). Pigs were then weighed at weaning (21 to 28 d of age) and then again at 8 weeks of age, when they left the rearing unit. Later all minipigs were weighed once each month and each minipig was weighed before it was sold.

On the Ellegaard farm the minipigs are housed in two different units. Minipigs from both units have the same ancestors, but there is no genetic exchange between the units. Thus, every unit is an independent sub-population with a specific environment. Because of these circumstances the calculations were made for each unit separately. It is then possible to detect potential differences in the growth curves between unit 1 and unit 2 due to environmental effects.



**Figure 1.** Number of body weight recordings per animal and corresponding number of animals for all minipigs used in this study

Within every unit the growth curve was modeled for each sex. The detailed numbers of analyzed animals and body weight records are shown in Table 1.

**Table 1.** Number of animals and records per sex and unit used in the calculations

Sex	Unit <sup>1</sup>	Animals	Records
Male	1	10,717	59,045
	2	6,676	37,012
Female	1	9,848	55,556
	2	6,463	38,112
Total		33,704	189,725

<sup>1</sup>independent sub-population.

There were no differences in the feeding regime in both units. The minipigs were provided a special minipig diet with 10.0 MJ ME/kg and 13.9 % CP of 250 to 500 g/d progressively fed from 2 to > 12 months of age to males. Females were fed approximately 80 % of the amount offered to males.

**Growth Models.** To estimate the body weight at a certain age four 3-parameter and three 4-parameter non-linear growth functions as well as 4 different polynomial growth functions were fitted to the minipig body weight data. The equations for the applied growth models are given in Table 2.

**Table 2.** Functions considered in this study for modeling the growth curve of the minipig

Model	Equations*	Parms <sup>#</sup>	Reference
Logistic	$W = \frac{a}{(1 + b \times e^{(-c \times t)})}$	3	(Fekedulegn et al., 1999)
Gompertz	$W = a \times e^{-e^{(b - (c \times t))}}$	3	(Wellock et al., 2004)
v. Bertalanffy	$W = \left[ \left( \frac{a}{b} - \frac{a}{b - W_0^{\frac{1}{3}}} \right) \times e^{\frac{1}{3} \times b \times t} \right]^3$	3	(Bertalanffy, 1957b)
Brody	$W = a \times (1 - b \times e^{(-c \times t)})$	3	(Fitzhugh Jr., 1976)
Richards	$W = \frac{a}{(1 + b \times e^{(-c \times t)})^{\frac{1}{m}}}$	4	(Fekedulegn et al., 1999)
Bridges	$W = W_0 + a \times (1 - e^{(-m \times t^p)})$	4	(Wellock et al., 2004)
Janoschek	$W = a - (a - W_0) \times e^{(-c \times t^m)}$	4	(Wellock et al., 2004)
Ali-Schaeffer	$W = d_0 + d_1 \left( \frac{t}{700} \right) + d_2 \left( \frac{t}{700} \right)^2 + d_3 \left( \ln \frac{700}{t} \right) + d_4 \left( \ln \frac{700}{t} \right)^2$	5	(Ali and Schaeffer, 1987)
Polynomials	$W = d_0 + \sum_{i=1}^r d_i \times t^i$	3 to 5	(Hadelar, 1974)

\*W = body weight; W<sub>0</sub> = initial weight of the animal in kg; a = mature weight of the animal in kg; t = age in days; b, c, m, p = parameters specific for the function; r = second to fourth order of fit; d<sub>0</sub> = intercept; d<sub>i</sub> = regression coefficients.

<sup>#</sup>number of parameters.

The Logistic (Robertson, 1908) as well as the Gompertz function (Gompertz, 1825) were developed in former centuries. They have three parameters in the equation with no flexible point of inflection. The von Bertalanffy function (Bertalanffy, 1957a), developed in 1957, is also a 3-parameter equation where the point of inflection lies at 30 % of the mature body

weight. A critical assumption of this function is that the anabolic processes of the body are proportional to the surface of the organism and the catabolic processes are proportional to the body weight. These conditions are not necessarily given in the growth of animals (Schönmuth and Seeland, 1994). The 3-parameter Brody function from 1945 also has a priori no point of inflection (Brody, 1945). The 4-parameter Richards function was developed in 1959 as an advancement of the Logistic and the Gompertz function (Richards, 1959). It has a flexible point of inflection and thus is suitable for the application to animal growth. The Janoschek function from 1957 (Janoschek, 1957) and the Bridges function from 1986 (Bridges et al., 1986) are also very flexible in their points of inflection and are mainly used to describe the postnatal growth of an individual. The Ali-Schaeffer function (Ali and Schaeffer, 1987) can be interpreted as a fractional polynomial of degree 4 which is mostly used in test day models for calculating lactation curves of dairy cows. Guo (1998) classified the Ali-Schaeffer function as a function of the mixed-log family. Linear models with a polynomial structure from second up to fourth order of fit were applied. Higher orders of fit did not achieve a significant influence on the fit of the growth curve ( $P < 0.001$ , F-Statistic, SS Type 1) and were therefore not considered in the analysis.

**Statistics and Model Comparison.** The estimation of the non-linear growth curves was carried out using the NLMIXED procedure of the SAS System Version 9 (SAS, 2002). The linear growth curves were calculated with the MIXED procedure of the same software. The models were compared by using Akaike's Information Criterion (AIC) (Akaike, 1973):

$$\text{AIC} = -2 \log \text{Likelihood} + 2(\text{number of parameters}).$$

This information criterion is useful for comparing models with different numbers of parameters. It is therefore more advantageous than the  $R^2$  which increases with increasing numbers of parameters in the models and thus, is not useful for the comparison of models with different numbers of parameters. The comparison of different non-nested models with this method determines which model is more likely to be correct and accounts for differences in the number of degrees of freedom. By using the ML method in the MIXED procedure, the AIC values obtained from both the MIXED and the NLMIXED procedure can be compared. The model with the smallest AIC value was chosen to be the best for fitting minipig body weight data.

For the model reduction from fourth to second order of fit in the linear polynomial functions the F-statistic was used.

### ***Comparison Minipig – Fattening Pig***

The results from Kusec (2001) were used for comparing the growth of the minipig with the growth of a fattening pig. This author analyzed the growth of 72 4-line crossbred barrows from an age of 9 to 26 weeks. The pigs weighed 23 kg at the beginning of the test and 138 kg (intensively-fed pigs) and 117 kg (restrictively-fed pigs) at the end of the experiment. The barrows had a Piétrain x Hampshire sire and a Large White x German Landrace dam. This crossbreed represents standard fattening pigs of the German Hybrid Pig Breeding Programme (Bundes-Hybrid-Zuchtprogramm, BHZP). The pigs in the experiment were fed in two different groups, an intensively-fed group and a restrictively-fed group. Additionally, two different genotypes of malignant hyperthermia-susceptible (**MHS**) pigs were examined within a feeding group. The MHS-gene has a positive effect on the carcass leanness but a negative effect on meat quality. The pig breeders have the option to choose sire lines of different MHS-gene status, whereas the dam lines in Germany are completely MHS-negative. The genotypes of the fattening pigs used in the study of Kusec (2001) were MHS-carrier (Nn) and MHS-negative pigs (NN). Both are often used genotypes in cross-bred fattening pigs in Germany. In the study of Kusec (2001) the growth curve for body weight was modeled with the Richards function so it can be compared with the growth curve of minipigs estimated with the Richards function in this study. On the basis of the estimated parameter values (Table 3) the body weight for fattening pigs were calculated for 0 to 700 d of age. For this calculation the parameter estimates of the Nn-genotype were used because there was no significant ( $P > 0.05$ ) difference between the parameter values of the two MHS-genotypes (G. Kusec, Faculty of Agriculture, Osijek, Croatia, personal communication).

First, the body weight of minipigs and fattening pigs at d 160 (**160d-W**) were compared. The 160<sup>th</sup> d is a typical day for slaughtering fattening pigs in performance tests in Germany.



**Table 3.** Parameter values of the Richards function for fattening pigs (Kusec, 2001) and minipigs (males of unit 1) used in this study

Parameter <sup>1</sup>	Fattening pigs		Minipigs
	Intensively fed	Restrictively fed	
a	220	160	53.47
b	0.054476	0.057374	-0.9628
c	1.38986	1.688707	0.00202
m	0.01	0.01	-0.7507

<sup>1</sup>a = mature body weight, kg; b = biological constant; c = maturing index; m = shape parameter determining the position of the inflection of the curve point.

The 160d-W from minipigs and fattening pigs was set to 100 % to achieve comparability. Second, the age was detected at which the pigs weigh 40 % of the predicted mature body weight. Again the particular body weight at 40 % of maturity (**40%-MW**) was set to 100 % for the minipigs and the fattening pigs to enable a comparison between the breeds.

To simplify the presentation only the results of male minipigs from unit 1 are used for the comparison of the minipigs with fattening pigs. Results for males in unit 2 and females in both units are not shown, but they were very similar to the results of males in unit 1.

## Results

### *Growth Curves Modeled over all Data*

Comparing the models by AIC values and the residuals showed the following results (Table 4). The polynomial function of third order of fit had the smallest AIC values for both sexes in unit 1. For unit 2 the smallest AIC values were achieved of the polynomial of fourth order of fit.

The examination of the polynomial models from second to fourth order of fit using the F-Statistic SS type 1 showed that the polynomials of second and third order of fit were significant ( $P < 0.01$ ) in unit 1 whereas the polynomial of fourth order of fit had no significant influence on the estimation of the growth curves for both sexes in unit 1. In unit 2 the polynomial of fourth order of fit had a significant influence ( $P < 0.01$ ) on the fit of the growth curve. Thus, the growth curves for unit 1 for both sexes were best fitted using a polynomial of third order of fit and the growth curves for unit 2 were best fitted by a polynomial of fourth order of fit.

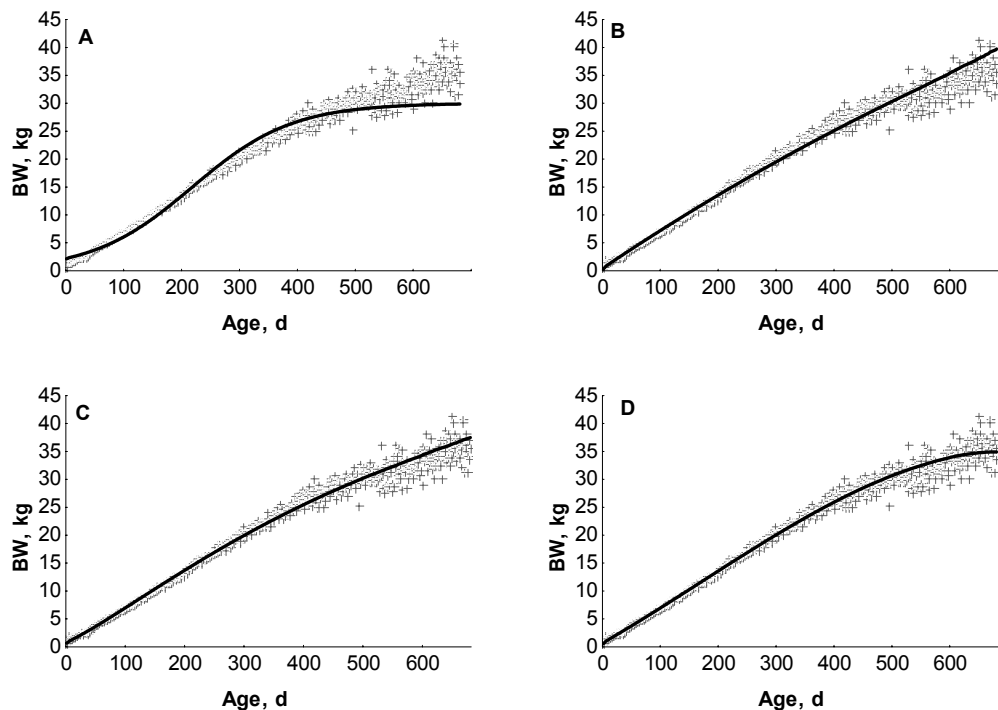
**Table 4.** Values of  $-2 L_m$  ( $L_m$  is the maximized log-likelihood), Akaike's Information Criterion (AIC), and residual variances (res.) for male and female minipigs of both units<sup>1</sup>

Sex	Male						Female					
	Unit1 <sup>2</sup>			Unit2 <sup>2</sup>			Unit1 <sup>2</sup>			Unit2 <sup>2</sup>		
Unit	-2 $L_m$	AIC	Res.	-2 $L_m$	AIC	Res.	-2 $L_m$	AIC	Res.	-2 $L_m$	AIC	Res.
Logistic	300,146	300,152	3.245	188,756	188,762	3.262	299,771	299,777	3.558	209,908	209,914	3.670
Gompertz	259,874	259,880	2.563	162,297	162,303	2.547	257,226	257,232	2.792	176,895	176,901	2.804
Bertalanffy	248,756	248,762	2.375	154,826	154,832	2.345	245,587	245,593	2.583	168,356	168,362	2.580
Brody	245,935	245,941	2.327	152,812	152,818	2.291	242,906	242,912	2.534	169,792	169,803	2.617
Richards	242,096	242,104	2.262	150,195	150,203	2.220	238,687	238,695	2.458	164,319	164,327	2.474
Bridges	242,415	242,423	2.268	150,346	150,354	2.224	238,931	238,939	2.463	164,480	164,488	2.478
Janoschek	246,106	246,114	2.330	152,588	152,596	2.285	243,274	243,282	2.541	168,597	168,605	2.586
Ali-Schaeffer	240,068	240,078	2.228	149,260	149,270	<b>2.195</b>	236,779	236,789	2.424	163,251	163,261	<b>2.446</b>
Polynomial, second order	217,176	217,184	2.319	135,475	135,483	2.284	208,923	208,931	2.612	144,233	144,241	2.622
Polynomial, third order	214,826	<b>214,836</b>	<b>2.227</b>	134,456	134,466	2.214	206,651	<b>206,661</b>	<b>2.415</b>	142,616	142,626	2.470
Polynomial, fourth order	214,826	214,838	2.246	134,270	<b>134,282</b>	2.204	206,650	206,662	2.453	142,368	<b>142,380</b>	2.455

<sup>1</sup>The lowest values for AIC and res. are printed in boldface in each column.

<sup>2</sup> Unit 1 and unit 2 represent independent subpopulations.

The smallest AIC value for the non-linear models was calculated for the 4-parameter Richards function in both units. If a minipig growth curve is modeled with a 3-parameter model, the Brody function will be implemented according to the AIC value. The Logistic function was definitely the model with the greatest AIC value. A graphical comparison of the Logistic, the Brody and the Richards function as well as the polynomial of third order of fit is given in Figure 2. In this figure only the results for males in unit 1 are displayed as an example without loss of generality, since curves of females and for males in unit 2 look very similar.

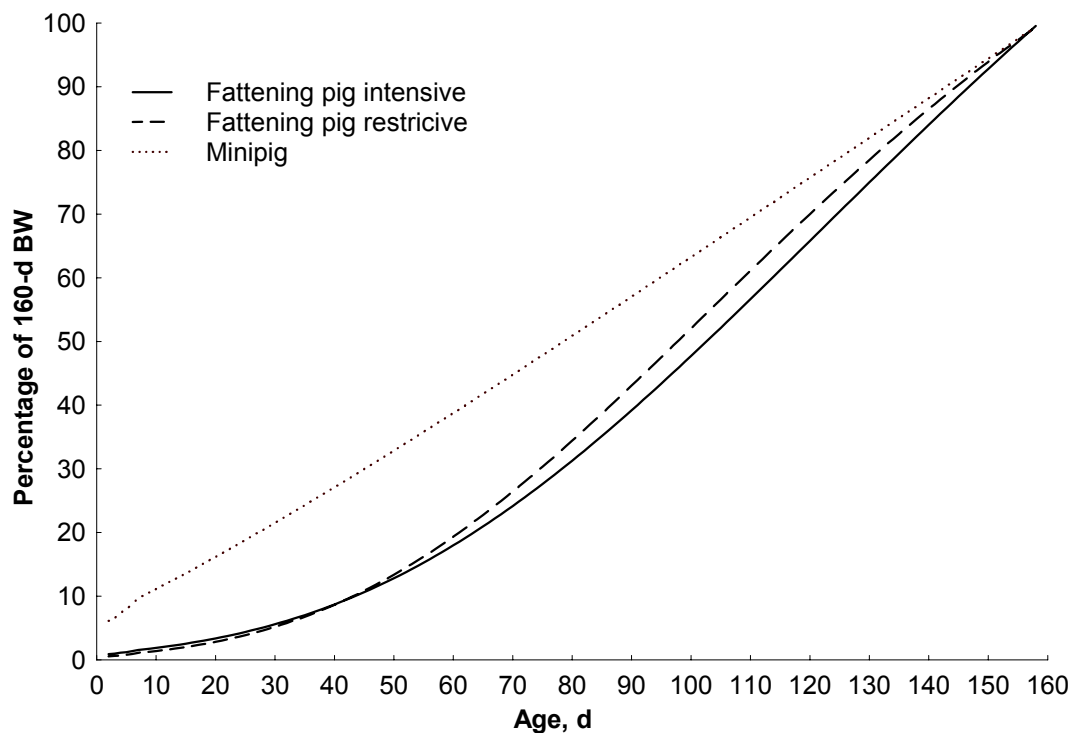


**Figure 2.** Growth curves of the Goettingen minipig for males in unit 1 as predicted by the Logistic (A), Brody (B), Richards (C), and third order polynomial functions (D)

By comparing all models on the basis of residuals the best fitting model for unit 2 was not the polynomial of fourth order of fit, but the Ali-Schaffer function. For unit 1 the polynomial of third order of fit had the lowest residuals. The Brody function was the best fitting 3-parameter function and the Richards function was the best fitting 4-parameter function on the basis of the calculated residuals for both units.

### Comparison Minipig – Fattening Pig

According to the calculated body weight for the fattening pigs and the predicted body weight for the minipigs from the Richards function, Figure 3 shows the relative body weight development of the pigs from birth to 160 d of age. The minipigs have an almost linear body weight development in this time period. The fattening pigs show very small body weights in relation to their particular 160d-W up to 50 d of age. Then after 50 d of age they have increasing body weights through to 160 d of age. The restrictively-fed pigs are characterized by a steeper slope of the curve after d 42 in relation to the intensively-fed pigs. Thus, compared to the intensively-fed pigs, they have greater ADG after 42 d of age.



**Figure 3.** Relative body weight development of male minipigs of unit 1 and normal, fattening pigs from birth weight to 160-d body weight (160d-W)

The birth weights of the analyzed breeds differ in a remarkable way in relation to the 160d-W. At birth and throughout birth to 160 d of age, the proportion of body weight to its 160d-W is greater in the minipig compared with the fattening pig.

The second comparative analysis determined the body weight development of minipigs and fattening pigs from birth to a stage of 40 % of maturity. The body weights and ages for minipigs and fattening pigs are shown in Table 5.

**Table 5.** Mature body weight and ages at 40% of mature body weight (40%-MW) of normal, fattening pigs and minipigs (males of unit 1) calculated with parameters of the Richards function

Item	Fattening pigs <sup>1</sup>		Minipigs
	Intensively fed	Restrictively fed	
Mature body weight, kg	220 <sup>1</sup>	160 <sup>1</sup>	53
40%-MW, kg	88	64	21
Age at 40%-MW, d	129	109	310

<sup>1</sup>Kusec (2001)

The minipigs need 2.4 times longer than the intensively-fed fattening pig to reach 40%-MW. In relation to their 40%-MW the minipigs have a greater birth weight than the fattening pigs. It can be observed that the minipigs have a nearly linear body weight development until the chosen degree of maturity (data not shown). Further, the minipigs can realize greater ADG from birth up to 50 % of age at 40% maturity in relation to the 40%-MW than fattening pigs. After 50 % of age at 40% maturity the body weight development of the fattening pigs increases more rapidly. Restrictively-fed fattening pigs have in all stages until 40 % of maturity a lower body weight in relation to their 40%-MW than the intensively-fed fattening pigs.

## Discussion

Modeling growth curves of animals is a necessary tool for optimizing the management and the efficiency of animal production. It is obvious that growth modeling has many advantages for meat producing animals (Schinckel and de Lange, 1996). As a consequence, many studies dealing with modeling of growth curves have used pigs (Bastianelli and Sauvant, 1997; Knap et al., 2003; Krieter and Kalm, 1989; Schinckel et al., 2003; Wellock et al., 2004; Whittemore, 1986), cattle (Brown et al., 1976; Lopez de Torre et al., 1992; Menchaca et al., 1996), and poultry (Knizetova et al., 1991b; Sengül and Kiraz, 2005). In the last few years it has become more and more popular to analyze the growth of special livestock, e.g., the Bolivian llama (Wurzinger et al., 2005) and the pearl gray guinea fowl (Nahashon et al., 2006) for providing improvement for their husbandry. Because of the increasing importance of the Goettingen minipig for medical research it is necessary to

analyze the body weight development of this breed for the well-founded derivation of required space for guidelines of laboratory animals and adjusted feeding regimens. The knowledge of growth pattern in minipigs also facilitates the creation of experimental designs.

The growth of the Goettingen minipig is not the same as the growth of pig breeds for meat production. Apart from the different mature body weight the body weight development of the minipig should be slower than the body weight development of normal pigs, mainly in the first year so that the mature body weight of the Goettingen minipig will be achieved later than the mature body weight of normal pigs. On the basis of growth parameters of the Richards function estimated in this study and in the study of Kusec (2001) the age at maturity was calculated for minipigs and intensively-fed fattening pigs. Minipigs are expected to have a constant mature body weight around 5 years of age while intensively-fed fattening pigs reach a constant body weight with approximately 4.2 years of age. Thus, the minipigs seem to reach maturity at an older age than fattening pigs. Body measurements, such as length and circumference of skeletal tissue, provide a more exact determination of maturity (Lawrence and Fowler, 2002) and these data should be included when there is a focus on size at maturity.

The application of different non-linear and linear functions to body weight data from Goettingen minipigs is the first study made for this species in such detail. The data set of the current study is unique based on the very large number of animals and body weight recordings over a wide range of ages. The results of the non-linear functions showed that the Richards function was the best for fitting the minipig data according to the AIC values. This is in agreement with Brown et al. (1976) who applied the Logistic, Gompertz, von Bertalanffy, Brody, and Richards function to body weight data of different cattle breeds. Brown et al. (1976) also noted that the Logistic model is worst for fitting their cattle body weight data. The Richards function was also considered as best by Knizetova et al. (1991a) for growth analyses in ducks and other poultry, like geese and chicken, after checking the Logistic, Gompertz and Richards function for the growth of poultry in other studies.

Krieter and Kalm (1989) applied the growth model developed from Schnute (1981) for estimating the growth curves of Large White and Piétrain pigs. The pigs were weighed weekly from 25 kg to 223 kg (Large White) and from 29 kg to 186 kg (Piétrain), respectively. In the model proposed from Schnute (1981) the non-linear growth functions Logistic, Gompertz, von Bertalanffy, Richards, and others like a linear, quadratic or expo-

nential function are included. Combining several models into a single model reduces the problem of comparing the different parameters used by each individual model. Intercepts, inflection points, and asymptotic size are no longer essential, although they can be identified easily if they occur. Krieter and Kalm (1989) found that the von Bertalanffy model had the lowest residual standard deviation compared with the Richards and the Gompertz function, which is not in agreement with the results of our study. A focus on the residuals of the non-linear models suggests that the Richards function is the best fitting model for minipig body weight data. Regarding all models, the polynomial of third order of fit was the best fitting model for the minipig body weight data from unit 1 and the Ali-Schaeffer function was the best model for unit 2.

The difficulty in comparing the results of this study with other studies dealing with pig growth lies in the different time periods that were examined. For minipigs the whole period of growth from birth to later ages is of interest, because the body weight at later ages is an important variable for breeding selection. Meat producing breeds like the Large White or Piétrain are observed from 30 to 105 kg body weight in the performance test, i.e., from 90 d of age at the beginning of the fattening period to 160 to 180 d of age at the end of the fattening period (ZDS, 2004). Castrated Large White pigs average 160 d of age at the end of the fattening period (VIT, 2005). Thus, the time between weaning and slaughter at 160 d is the best time to measure growth rate in fattening pigs.

An extreme example is the study of Schinckel et al. (2003), who modeled the growth of pigs from birth to 60 d of age. The authors also applied the Gompertz and the Bridges functions, additionally the Michaelis-Menten equation and an exponential linear quadratic equation of form  $W_{ij} = \exp(b_0 + b_1t + b_2t^2) + e_{ij}$ , where  $W_{ij}$  is body weight,  $t$  is age,  $b_0$ ,  $b_1$  and  $b_2$  are regression coefficients and  $e_{ij}$  is the residual term. The different models were compared by using the residual standard deviation. The authors concluded from their results that the exponential linear quadratic equation is the best fitting model for estimating the growth of pigs from birth to 60 d of age. However, the authors mentioned a lack of fit for the exponential equation, resulting in an inaccurate prediction of the birth weight of each pig, and that probably a more complex function is needed.

When modeling growth of the fattening pig numerous studies deal with the pattern of compositional growth (Bastianelli and Sauvant, 1997; Whittemore, 1986). In this case the growth curves for protein growth or lean growth, respectively, and fat growth are modeled separately (Knap et al., 2003), often combined with different levels of feed intake. There-

fore the growth curve of body weight in the time period of interest has to be modeled. The relationship of the body component (e.g., protein) to the body weight has to be fitted. Development of growth curves for body components (e.g., protein and fat) can be a useful tool for management of pork production, because it can aid in determining the best time to slaughter animals and depending on genotype, feed intake can be predicted (Schinckel and de Lange, 1996).

Modeling different growth fractions separately is not necessary for the minipig. The minipig is a laboratory animal and is never used for commercial meat production. If body components were modeled separately it could be used to adjust the feeding regimen (e.g., feeding restrictions) to prevent the minipig from becoming too heavy.

Using estimates from the Richards function, a difference in body weight development between minipigs and fattening pigs is observed. From d 0 to 160 d of age, the minipig growth curve is approximately linear (Figure 4). This result is consistent with the minipig growth analysis conducted by Brandt et al. (1997) who modeled the growth of 283 minipig sows from birth to 1,100 d of age with the Boltzmann function. In contrast, the fattening pigs have very low ADG in the beginning and greater ADG from d 50 to the end of the time period. Thus, the growth curve of a fattening pig is s-shaped. Applications of other growth functions apart from the Richards function lead to similar results as far as these functions have a flexible point of inflection. All functions show a linear growth of minipigs in the first year except the Logistic function which has a fixed point of inflection. Thus, it is also expected that the trajectory of the growth curve of fattening pigs is s-shaped when modeling the growth with growth functions other than the Richards function as far as a flexible point of inflection exists.

It is obvious that the selection on greater ADG in fattening pigs focuses on the last 67 % of the period from d 0 to 160 d of age. The minipig growth curve should be changed into a lower level (i.e., the asymptotic body weight should be lower). A change from linearity to a more s-shaped trajectory would be advantageous for the first part of the growth curve. If this aim could be achieved, it would be possible to produce minipigs with very small ADG and as a consequence smaller body weight in the first few months of their lives, which is the main period for starting medical or pharmaceutical experiments. On the basis of genetic analyses that will be conducted the best time for selecting minipigs for lower body weight will be determined. Additionally, it could be determined if a change of the minipig growth curve is possible.



The modeling of growth curves of the Goettingen minipig with different non-linear and linear functions is a useful tool for the derivation of space and food requirements at different ages. Based on the current study, it is also possible to apply the best fitting models (i.e., linear polynomials) for the estimation and analysis of genetic parameters with random regression models concerning the breeding goal 'low body weight', which should be obtained especially in the juvenile period which is the main period for marketing.

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### **3<sup>rd</sup> CHAPTER**

#### **Estimation of genetic parameters for body weight of the Goettingen minipig with random regression models**

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## **Estimation of genetic parameters for body weight of the Goettingen minipig with random regression models**

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### **Abstract**

The Goettingen minipig is a laboratory animal especially developed for medical research. For easy and comfortable handling during experiments, and to minimize costs, a low body weight is essential. To breed for an even smaller minipig, genetic parameters for body weight were estimated using a random regression model (RRM). The RRM was calculated using random animal, common litter environment and permanent environment effects, respectively. Regressions for the random effects in the RRM were modeled using Legendre polynomials from second to fourth order of fit in different combinations. The model was applied to a data set which focused on the time period from 30 to 400 d of age. Eight age classes were built to consider heterogeneous residual variances. The heritabilities were moderate and ranged from 0.211 (375 d of age) to 0.2542 (275 d of age). The variances initially decreased and then increased towards the end of the examined time period for permanent environment and litter effect. Genetic and phenotypic correlations between body weights in different age classes decreased with increasing distance between age classes. The major eigenfunction showed positive values throughout the whole trajectory, i.e. a selection for low body weight has positive effects on this trait throughout the whole range of time. On the basis of the estimated genetic parameters a breeding scheme can be created to develop genetically smaller Goettingen minipigs in the future.

### **Keywords**

Body weight, genetic parameters, Goettingen minipig, random regression

## Introduction

The Goettingen minipig is a laboratory animal which has a widespread popularity in medical and pharmaceutical research because of its shared anatomic and physiologic characteristics with humans. In general, swine are becoming more and more important as non-rodent models in medical experiments. Major advantages are that pigs are not considered companion animals as are dogs and they do not have physical similarities or phylogenetic proximity to humans as do primates. With respect to ethics and animal welfare, pigs therefore are a much less disputed model species in medical research (Gad, 2007). The most important advantage of the minipig in comparison to normal pigs is the smaller body size and the resulting low body weight of 35-45 kg for adult minipigs (Bollen et al., 1998). The low body weight is a necessary trait because handling in medical experiments is more easily facilitated and the costs for housing, feeding and dosing are lower. At present there is no line of minipig that has been selected for a low body weight and the inheritance of low body weight of Goettingen minipigs at different ages is still unknown. It is necessary to have a genetically small minipig, not simply a pig of reduced weight from restricted feeding (Brandt et al., 1997).

Body weight is a trait where the phenotype of an animal can be represented by a continuous function of time. Thus, this trait is characterized by a trajectory with a theoretically infinite number of measurements. Therefore, an appropriate model is one which considers a complex covariance structure. In the infinite-dimensional approach, the covariance structure is modeled as a covariance function (**CF**) (Kirkpatrick et al., 1990). The CF quantifies the variation of the individual growth curves about the population mean. A useful tool for the estimation of CF is the random regression model (**RRM**) (Van der Werf, 2001).

The aims of this study were the estimation of genetic parameters for the trait *body weight* with a RRM and conclusions about prospects of selection response for low body weight.

## Data and Methods

Body weight data were provided from Ellegaard Goettingen Minipigs ApS, Denmark, where two sub-populations of the Goettingen minipig base population are housed in two units which are entirely separated from each other, both physically and with respect to

gene flow between them. The data were acquired from 1995 to 2005. The minipigs were weighed routinely at various intervals, without provision for fasting before weighing. All pigs were weighed at birth, then at weaning (21 to 28 d of age) and again at 8 weeks of age, when they left the rearing unit. Later, all minipigs were weighed once each month, and each minipig was weighed before it was sold. Unlike slaughter pigs minipigs are not kept until a certain age or weight, but are sold for different purposes at very different ages. Therefore, the number of available weights per pig varies considerably.

In total the original dataset contained 199,764 body weight records of 33,749 animals. Because of scarcity, body weights measured after 400 d of age were excluded from the analyses. Outliers of the data set were also excluded. This resulted in a total of 180,092 body weight records of 32,510 animals. A data set with a focus on 30 to 400 days of age was prepared out of this data for the RR analysis. The body weights from day 0 to day 29 were excluded, because they are influenced by the parity and the lactation length of the sow and can not be classified as independent body weight traits like those after weaning.

The residuals, or the so-called temporary environmental effects, should not be assumed to be homogeneous over the observed range of time (Schaeffer, 2004). After a graphical analysis of the residuals, they were considered independently distributed with heterogeneous variances. Changes in the residual variances with age were modeled as a step function with different age classes. Within every age class equal residual variance was assumed. Eight age classes were built for the consideration of heterogeneous residual variances (Table 1).

**Table 1.** Age classes, age range (in d), number of records, mean body weight (in kg) and variance of body weight (in kg<sup>2</sup>) per age class

Age class	Age range in d	n records	Mean weight in kg	Variance of weight in kg <sup>2</sup>
1	30-60	5,792	3.33	1.04
2	61-100	5,761	5.28	1.54
3	101-150	5,855	8.36	3.24
4	151-200	5,821	11.84	5.61
5	201-250	5,639	15.25	7.82
6	251-300	4,105	18.69	9.06
7	301-350	3,012	21.82	10.14
8	351-400	2,038	24.86	10.48

Preliminary analyses with completely unstructured data and data sets with less than 5 measurements per animal resulted in no convergence, thus every animal had at least 5 weight recordings with only one record per age class. Animals with less than 5 body weight measurements were excluded from the analysis. The body weight record measured at an age that was closest to the average age per age class was accounted for in the analysis. This resulted in 38,023 records of 6,713 animals.

For the analysis with RRM, Legendre polynomials (**LP**) for the regression on age at weighing were used for modeling the random effects. Therefore, the age at which the body weight recordings were taken had to be rescaled to a standardized age  $t^*$  for the orthogonal functions, using the formula:

$$t^* = \frac{2(t - t_{\min})}{(t_{\max} - t_{\min})} - 1,$$

where  $t_{\min}$  is the youngest age, here 30 d of age, and  $t_{\max}$  is the oldest age, here 400 d of age, respectively. The random regression animal model was:

$$y_{ijkl}(t) = \mu + S_i + U_j + Y_k + \sum_{r=1}^3 \beta_r t^r + \sum_{s=1}^S \alpha_{sijkl} \phi_s(t^*) + \sum_{s=1}^S \gamma_{sijkl} \phi_s(t^*) + \sum_{s=1}^S \rho_{sj} \phi_s(t^*) + \varepsilon_{ijkl}$$

where  $y_{ijkl}(t)$  = weight of animal  $l$  at age  $t$  within sex  $i$ , unit  $j$  and birth year  $k$ ;  $S_i$  = fixed effect of sex  $i$ ;  $U_j$  = fixed effect of unit  $j$ ;  $Y_k$  = fixed effect of birth year  $k$ ;  $\beta_r$  = fixed cubic regression coefficient;  $t$  = age in d;  $t^*$  = age standardized to the range -1 to 1;  $\phi_s$  = value of the  $s$ -th LP at standardized age  $t^*$ ;  $\alpha_{sijkl}$  = random regression coefficient for additive-genetic effects;  $\gamma_{sijkl}$  = random regression coefficient for permanent environmental effects;  $\rho_{sj}$  = random regression coefficient for common environmental effects for litter; and  $\varepsilon_{ijkl}$  = random measurement error.

The fixed regression with the fixed effects sex, unit and birth year was calculated with a polynomial of third order of fit. This polynomial model was chosen as that with the best fit after applying different linear and non-linear functions to growth data of Goettingen minipigs (Köhn et al., 2007). The random regression coefficients for additive-genetic effect, permanent environmental effect and common litter environmental effect, were fitted with LP from quadratic (LP 2) with three terms to quartic (LP 4) LP with five terms. Every possible combination of LP for the random effects was calculated.



The final pedigree contained 35,066 animals. The 6,713 animals that were represented in this study were offspring of 332 sires and 1,030 dams.

Covariance components for the random regression coefficients estimated via restricted maximum likelihood were obtained by using VCE-5 (Kovac et al., 2002). With the procedure IML from the software package SAS (SAS, 2002), the eigenfunctions with corresponding eigenvalues were calculated for the covariance components of the random regression coefficients. Eigenfunctions and eigenvalues can provide insight into the potential for genetic change in the average growth curve of the whole population. They are calculated from the covariance matrix of the random animal effects. To each eigenfunction a specific eigenvalue is associated. This eigenvalue represents the amount of variation explained by the corresponding eigenfunction. Accordingly, a large eigenvalue represents considerable genetic variation for pattern of growth and changes in the growth curve that can be modified by selection (Bermejo et al., 2003).

It is outlined by Jamrozik and Schaffer (2002) that different test criteria like Akaike's information criterion or the information criterion based on Bayes statistics rank models in a different way. Due to the fact, that it is unclear which criterion is the best for choosing the right model in this study, the model comparison was carried out by using the estimated mean squared error, as was done by (Meyer, 2005b).

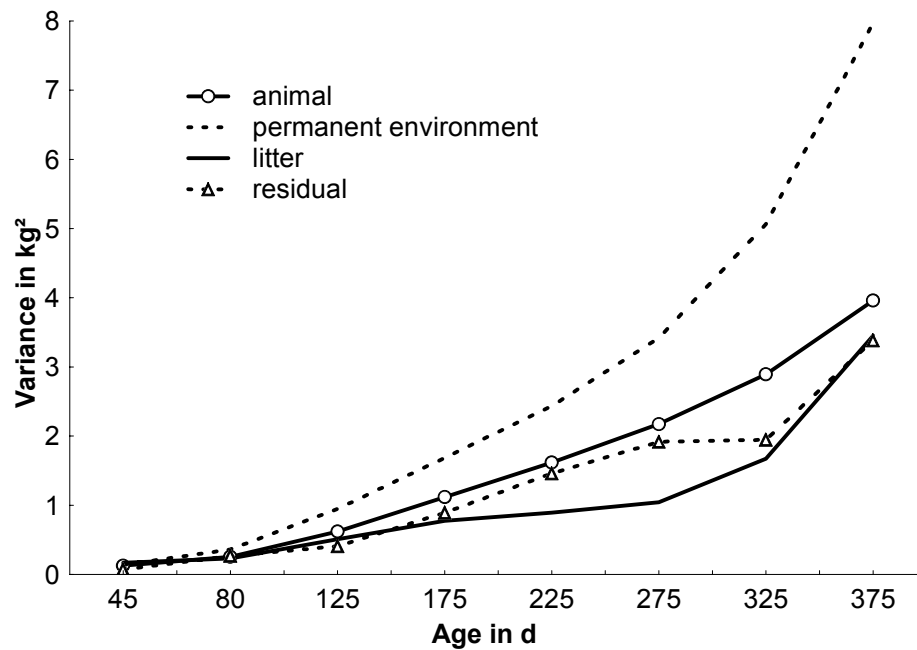
## Results

After examining the estimated variances and variance proportions for all models, the best fitting RRM for both data sets was the model with a polynomial of third order of fit for the fixed effects and LP of second order of fit (LP 2) for all random effects. In the following, only the results of this model are presented.

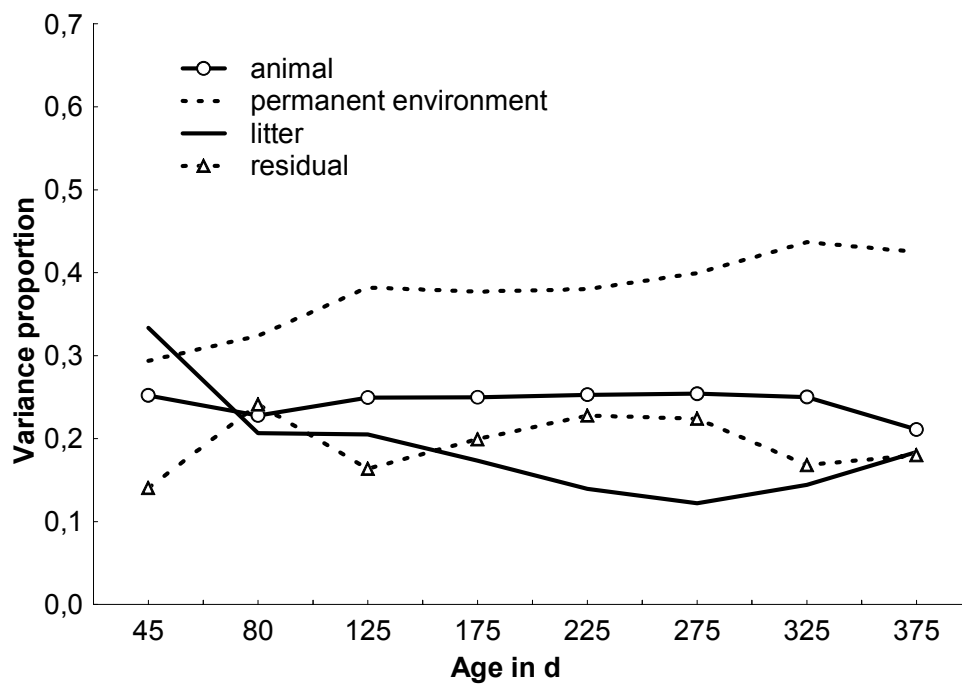
The variances of random animal, litter, permanent environment, and residual effect increased steadily over the examined time period (Figure 1).

The heritabilities increased up to 275 d of age with a lower value at 80 d of age and decreased afterwards (Figure 2). The proportions of variance for the litter effect decreased continuously up to 275 d of age and increased again afterwards. For the permanent environmental effect the proportions of variance increased steadily. The proportions of the

residual variance increased and decreased over the examined time period but on a more or less constant level between 0.14 (45 d) and 0.24 (80 d).

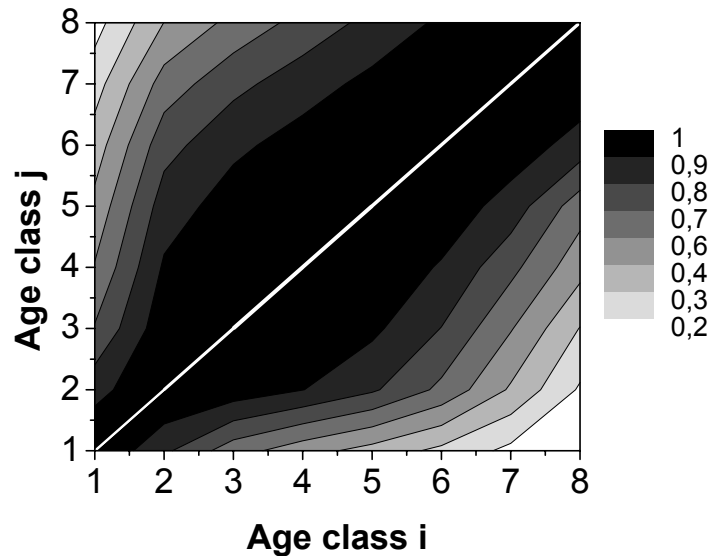


**Figure 1.** Variances (in kg<sup>2</sup>) for random and residual effects estimated with RRM (LP 2)



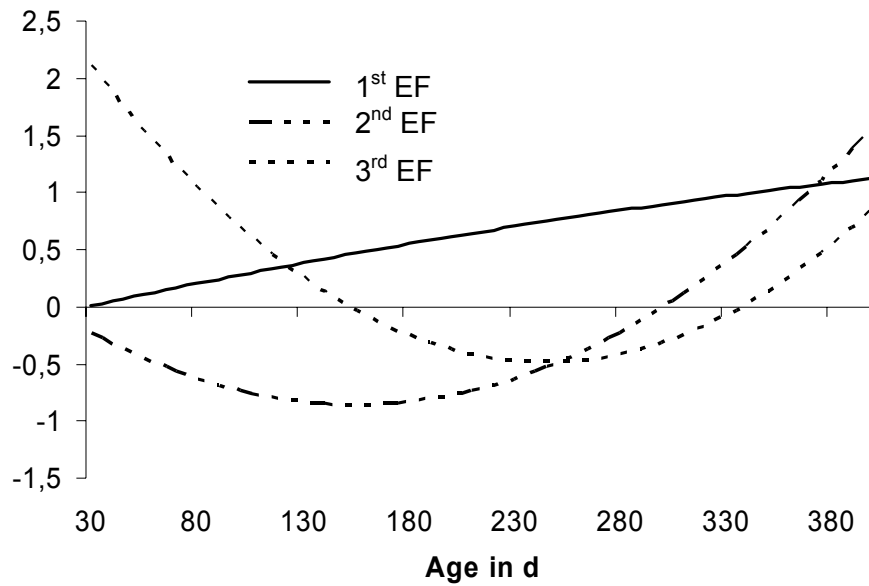
**Figure 2.** Variance proportions for the random and residual effects estimated with RRM (LP2)

As expected, the genetic and phenotypic correlations between body weights in different age classes decreased continuously with increasing distance between the age classes (Figure 3).



**Figure 3.** Genetic (above diagonal) and phenotypic correlations (below diagonal) between body weights in different age classes

The estimates of the first eigenfunction were positive throughout (Figure 4). As a consequence, selection on the trait *low body weight* at any age will change body weight in the period of 30 to 400 d of age in the same direction. The first eigenvalue explained 89.93 % of the genetic variation. As it is outlined by Kingsolver et al. (2001) eigenvalues indicate the amount of variance explained by its associated eigenfunction. The second eigenfunction explained 9.45 % of the genetic variation. In this case, a selection before 305 d of age on the trait *low body weight* leads to a negative effect on this trait from 305 to 400 d of age. The third eigenfunction explained only 0.62 % of the genetic variation and can be neglected. It can be concluded that the genetic variation associated with the second and third eigenfunction is small compared to the genetic variation associated with the first eigenfunction.



**Figure 4.** Eigenfunctions (EF) for the random animal effect estimated with RRM (LP 2)

## Discussion

The importance of Goettingen minipigs in medical research is increasing every year. To ensure a genetically small pig and to decrease body weight of Goettingen minipigs in the future, a breeding strategy for the trait *low body weight* has to be developed. This is the first genetic study made for body weight of Goettingen minipigs in such detail. Additionally, this data set is unique in pig research due to the high number of animals that had at least five weight recordings over a wide time range. If the analyzed trait is measured along a trajectory, which is the case with body weight measurements, the covariance structure should take the ordering of the measurements in time into account. The RRM is able to give the covariances of a trait that is measured at different ages as a function of these ages. There is no need for an adjustment of ages with this model and, as a consequence, errors associated with an adjustment are avoided (Albuquerque and Meyer, 2001).

The main advantages of RRM in comparison to the conventionally used multiple trait model are a smaller number of parameters to describe longitudinal measurements, smoother covariance estimates, no regular measurement schedules are needed, as well as the possibility to estimate covariance components and predict breeding values at any point along the trajectory. RRM enable modeling and investigation of growth curves as a function of age for individual animals.

RRM have been used for the analysis of test day records in dairy cattle (Jamrozik et al., 1997; Schaeffer and Dekkers, 1994; Van der Werf et al., 1998; Veerkamp and Thompson, 1999). Test day records are a very typical example for a repeated measured trait in animal breeding, since milk yield per test day changes during the lactation. The same can be observed for body weights of animals which are also changing gradually until a plateau at maturity is reached (Arango and Van Vleck, 2002). Thus, growth is a longitudinal process with many measurements that are highly correlated. Many studies used RRM for the estimation of genetic parameters of growth in beef cattle (Albuquerque and Meyer, 2001; Arango et al., 2004; Bohmanova et al., 2005; Krejcova et al., 2005; Meyer, 1999, 2000, 2001; Nobre et al., 2003b) and sheep (Fischer et al., 2004; Lewis and Brotherstone, 2002). In the last few years RRM were also applied for the investigation of genetics in pig growth and feed intake (Huisman et al., 2005; Huisman et al., 2002; Malovrh, 2003).

When including random effects in the model, the total variation can be separated in within- and between-animal variation. Normally, non-linear functions like the Gompertz, von Bertalanffy, Brody and Richards function are used to describe growth curves in pigs (Köhn et al., 2007). They are preferred because of their well-founded biological meaning. When using non-linear functions, the growth curve has to be modeled and the growth parameters of the particular function have to be estimated for each animal. In a second step, the estimation of environmental effects and variance components has to be conducted. The problem is that the information on relatives is not considered while estimating the growth curve. Further, errors which are typically correlated in repeated measures analysis are not taken into account with these traditional approaches (Albuquerque and Meyer, 2001). These disadvantages are the reasons for choosing linear polynomial models for the estimation of variance components with RRM. Kirkpatrick et al. (1990) proposed to use orthogonal polynomials of standardized units of time as covariables for the random regressions. The most common type of orthogonal polynomials used is the LP. In this study, a polynomial of third order was used for modeling the fixed part of the regression and LP were used to model the regressions of random effects.

The heritabilities for body weight were moderate in this study (Figure 2). The decrease for the estimated heritability at 80 d of age is due to high residual variance ratios at this age. This can be explained by a lower number of analyzed weight recordings in the second age class and a higher variance in weights compared to the first age class.

Huisman et al. (2002) calculated lower heritabilities of 0.17 (70 d of age) to 0.18 (190 d of age). They estimated the heritabilities with the weight data of 1,315 boars. The RRM was fit as a sire model and not as an animal model as in this study. Therefore, the results are not completely comparable with our results. In the study of Malovrh (2003) 3,819 boars of 4 German pure-bred lines for fattening pigs were weighed six times in an age range from 30 to 167 d of age. A RRM with animal, litter and permanent environment as random effects was applied. In the study of Malovrh (2003), the estimated heritabilities were higher than in our study. They ranged from 0.30 at 31 d of age to 0.40 at 145 d of age. The proportion for the litter effect decreased over time, as was found in this study.

Additionally, Malovrh (2003) tested the influence of maternal genetic effect on pig growth. She found out, that the maternal genetic effect accounted for only a small proportion of variance compared to the other random effects. Thus, the maternal genetic effect can be neglected in growth studies for pigs if the pigs are weaned at an age of 21 to 28 d. However, the maternal genetic effect on growth traits has to be included in the model for growth analysis in sheep and beef cattle. Their offspring are weaned at later ages and the influence of the dam is more important for their growth development.

Another important fact is the exclusion of birth weight in the analysis. Implausible values of variance components often occur at extreme ages like at birth. This is mainly the problem with high order polynomials (Meyer, 2005a). Thus, including birth weights increased the order of fit for the best fitting polynomial model in a significant way in the study of Meyer (2001). Apiolaza et al. (2000) also mentioned, that RRM have problems of fitting data with small variances as it is typical for birth weights. So it is assumed that prenatal growth underlies a different growth process than postnatal growth. The study of Lewis and Brotherstone (2002) supports this hypothesis. Their investigation of genetic parameters for growth in sheep from 2 to 159 d of age lead to the conclusion that live weight in early ages seems to be under different genetic control than live weight in later ages.

The estimation of genetic parameters with RRM also provides an insight into the effects of selection across the growth trajectory by examining the eigenfunctions and eigenvalues. In this study the first eigenfunction had the highest associated eigenvalue. It explained 89.93 % of the genetic variation. Because of low values for the second and third eigenfunction it is sufficient to focus on the first eigenfunction. It indicates that selection between d 30 to d 400 changes the pattern of growth in the same direction, i.e. selection on

low body weight at d 30 will also lead to a low body weight at d 400. Thus, a successful selection on low body weight is possible.

As it is outlined by Nobre et al. (2003a) RR analysis requires structured data. Otherwise a poor fit for some curves modeled with RRM may be the consequence. Thus, for the estimation of genetic parameters with RRM on the basis of weight recordings with an uneven distribution as it is given in original, not adjusted data sets with minipig body weights, an adjustment of the results based on estimates from multiple trait models and literature information could be necessary. Another problem is a possible poor fit of growth curves estimated with RRM using LP. LP require large data sets with an almost homogeneous distribution of weight recordings for a successful estimation of variance components (Misztal, 2006). Points on the growth curve estimated with LP on the basis of only a few records very often contain artifacts. This is especially the case at the extremes of the growth curve. A possible alternative to LP is the use of splines. Splines are piece-wise polynomials, i.e. curves modeled from pieces of polynomials of low degrees and joined together at knots (Meyer, 2005a). They are able to estimate genetic parameters in a more robust way even if the distribution of weight recordings is very heterogeneous. However, with this method other problems do occur. A lack of smoothness for the predicted breeding values can be observed and the number and position of the knots have to be chosen very carefully to avoid artifacts (Misztal, 2006). Nevertheless, Iwaisaki et al. (2005) report a simpler implementation of RRM with splines when compared to LP.

On the basis of the results of this study it is possible to construct a breeding scheme with a focus on the reduction of body weight. As it is outlined by Brandt et al. (1997) there is a good potential for the selection on low body weight due to moderate heritabilities and a high genetic variation in body weight especially in later ages. This conclusion is also supported by the results of this study. Therefore, breeding progress for the trait *low body weight* is expected.

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## **4<sup>th</sup> CHAPTER**

### **Breeding for low body weight in Goettingen minipigs**

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## Breeding for low body weight in Goettingen minipigs

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### Abstract

The Goettingen minipig is a laboratory animal with increasing popularity in medical research. To get a genetically smaller minipig, a new breeding scheme with a focus on weight reduction has to be developed. Therefore, 19,505 body weight measurements of 3,461 Goettingen minipigs were analyzed with a multiple trait model (MTM) and a random regression model (RRM) for the estimation of genetic parameters. Heritabilities were moderate with slightly higher values estimated with the RRM. Genetic correlations between body weight measurements at different ages were decreasing with increasing time lag between the measurements. An operational breeding goal for *relative weight reduction* (*RWR*) is suggested in which the weight reduction in each age class is expressed as per cent of the actual body weight and is weighted according to the proportion of animals sold in this age class. Expected genetic progress was calculated for two different selection ages (80 and 150 d). Selection at age 150 d leads to an expected genetic progress of 3.9 % *RWR* per year. And it is shown how the selection for *RWR* will modify the shape of the growth curve. On the basis of these results, a new breeding scheme with a focus on weight reduction can be implemented, which also has to account for correlated undesirable effects, like decline of fertility and increased rate of inbreeding.

### Keywords

Body weight, genetic parameters, Goettingen minipig, growth curve, selection

## Introduction

Animal models are essential for assessing the safety of new pharmaceuticals or new surgical techniques. Usually, two different species have to be used as toxicological models in pharmacology, a rodent like mice or rats and a non-rodent species. As a non-rodent species, pigs have many advantages compared to dogs, which are at the moment still the most widely used non-rodent species in medical research. Pigs show high similarities to humans concerning the cardiovascular system, the gastro-intestinal tract, the lung, kidney, liver, the immune system, and the skin and skeleton (Holtz and Bollen, 1999). A main point which makes the pig more advantageous than the dog is that pigs are usually not used as pets and therefore the emotional barrier to use pigs in medical experiments is much lower than in dogs (Gad, 2007). Since pigs are difficult to handle due to their large size, special small pig breeds were developed to facilitate the handling. The Goettingen minipig was bred at the University of Goettingen in the 1960's. It combines the advantageous characteristics of pigs with a small size and therefore is of increasing popularity as an animal model for pharmaceutical and toxicological studies.

In drug development and testing, the test compounds are always administered per kg body weight. Since especially in the early phases of testing the costs per weight unit of compound may be extremely high, a low body weight of an experimental animal is very desirable and in many cases will be the dominating criterion for the choice of the species to be used. Since the average adult body weight of a Goettingen minipig is 35-45 kg (Bollen et al., 1998) compared to the adult body weight of the often used beagle dog of 18 kg, this difference may abolish the otherwise more attractive features of the Goettingen minipig, especially its similarity to humans in many biological criteria. This similarity is still given even so the body weight difference between humans and minipigs is increased after breeding for a smaller minipig. However, for analyzing special diseases like obesity or diabetes Goettingen minipigs with typical characteristics for the certain disease can be provided.

Besides the Goettingen minipig base population in Germany there are two populations in Denmark and one population in the USA. In neither of the populations selection for low body weight is carried out at the moment, despite the customers' demand for an even smaller minipig for easy handling and low costs of dosing, feeding and housing. As previous studies showed, it is in principle possible to select for a genetically small minipig (Brandt et al., 1997).

Objectives for breeding differ in many ways between Goettingen minipigs and slaughter pigs (and most of the other farm animals). The most obvious difference is that in the minipig the objective is to reduce the weight gain per time unit while in the meat producing species higher daily gains are desirable. Another special characteristic is that Goettingen minipigs are sold at all ages, from weaned piglets to adult animals, depending on the specific research topic of the end user. While most minipigs used in toxicology and drug testing (which is the main use) are purchased at age 4 to 6 months, significant numbers are sold in other age groups. Also, the time span of the minipigs used in experiments varies from a few days to long term studies over one year or more. The third characteristic is that it is virtually impossible to assign a reasonable economic weight to the body weight. While in some fields of application (like experimental surgery) body weight is essentially meaningless as long as it stays within a given wide range, a weight reduction of one kilogram in the early phase of toxicology trials may literally save thousands of euros (strongly depending of the cost of the synthesis of the compound to be tested). If compound availability is a quantitative problem, smaller animals requiring lower doses will even reduce the time to market for the drug to be developed which can have an enormous economic impact.

The aims of this study were the estimation of genetic parameters, the prediction of breeding values for body weight and the calculation of genetic progress dependent on the age at selection. Genetic parameters were estimated using a multiple trait model (**MTM**) and a random regression model (**RRM**).

While it is obvious that a smaller minipig would be advantageous in many applications, the definition of an operational breeding goal needs to be discussed and a suggestion will be made in this study. Based on this composite breeding objective we estimate the achievable genetic gain per year and discuss different aspects and eventual obstacles of a practical implementation of the suggested breeding scheme.

## **Data and Methods**

Body weight data were provided from Ellegaard Goettingen Minipigs ApS, Denmark, where two sub-populations of the Goettingen minipig base population are housed in two units. Both units are completely separated from each other, both physically and genetically. Analyzed body weights were measured from 1995 to 2005. The minipigs were weighed

routinely at birth, then at weaning (age 21 to 28 d) and again at age 8 wk, before leaving the rearing unit. Later, all minipigs were weighed once each month, and each minipig was weighed before it was sold. Because minipigs are sold for different purposes at very different ages, the number of available measurements per pig varies considerably.

In total the original dataset contained 199,764 body weight measurements of 33,749 animals. Because of scarcity, body weights measured after 700 d of age were excluded from analyses. Outliers of the data set were also excluded using the studentized residual as an analyzer for the influence of every single observation on the parameter estimates of a normal regression (Belsley et al., 1980). This resulted in 180,092 body weight measurements of 32,510 animals.

A data set with a focus on 30 to 700 days of age was extracted out of this data for the analysis with RRM and MTM. Body weights from day 0 to day 29 were excluded, because of an influence by the parity and the lactation length of the sow. These body weights cannot be classified as independent body weight traits like those after weaning because of the mentioned influence of parity and lactation effects. As shown by Oldigs (1986), birth and weaning weights cannot be used for the prediction of weights at later ages. Compared to the previous study where genetic parameters for a time period of 30 to 400 d were estimated (Köhn et al., 2007a), the time period up to 700 d was chosen in this study to get additional genetic parameters for body weight at later ages and to analyze the genetic correlations between body weight measurements at early and later ages. These estimates are needed to build up a breeding scheme which considers also body weight in older minipigs. The observed time period is the main period to select minipigs for breeding, whereas an early selection is desirable, because most of the minipigs that are sold at 3 to 6 months age are not longer available for breeding.

Variances of residuals were heterogeneous and changes in the residual variances with age were modeled as a step function with different age classes (Köhn et al., 2007a). Within every age class equal residual variance was assumed. Table 1 gives an overview of the eight age classes that were built for the consideration of heterogeneous residual variances. Preliminary analyses with completely unstructured data and data sets with less than 5 measurements per animal resulted in no convergence for RRM, thus every animal was required to have at least 5 weight measurements with only one measurement per age class. Animals with less than 5 body weight measurements were excluded from the analysis. The body weight measured at an age that was closest to the average age per age class was

accounted for in the analysis. This resulted in 19,505 records of 3,461 animals. Each measurement per age class was treated as a different trait resulting in a MTM with 8 traits.

**Table 1.** Age classes, age range (in d), number (n) of records, mean body weight (in kg) and variance of body weight (in kg<sup>2</sup>) per age class

Age class	Age range (in d)	n	Mean weight ( in kg)	Variance of weight (in kg <sup>2</sup> )
45	30-60	3,043	3.28	1.08
80	61-100	3,031	5.30	1.65
150	101-200	3,448	8.93	4.53
250	201-300	3,268	15.71	9.38
350	301-400	3,049	22.52	12.13
450	401-500	1,842	27.96	11.29
550	501-600	1,134	31.98	10.80
650	601-700	690	34.86	10.98

The complete pedigree contained 35,066 animals. The 3,461 animals that were included in this study were offspring of 295 sires and 794 dams.

The multiple trait animal model used was:

$$y_{ijklmn} = \mu_m + S_{im} + U_{jm} + Y_{km} + \sum_{r=1}^{c_m} \beta_{mr} (t_{ijklm} - \bar{t}_m)^r + a_{ijklmn} + l_{jlm} + e_{ijklmn}$$

where  $y_{ijklmn}$  = weight in age class m of animal n within sex i, unit j, birth year k, and litter l;  $\mu_m$  = population mean in age class m;  $S_{im}$  = fixed effect of sex i;  $U_{jm}$  = fixed effect of unit j;  $Y_{km}$  = fixed effect of birth year k;  $\beta_{mr}$  = fixed regression coefficient for linear ( $c_m = 1$ ) and quadratic ( $c_m = 2$ ) polynomials;  $\bar{t}_m$  = average age per age class m;  $t_{ijklm}$  = age at weighing per age class;  $a_{ijklmn}$  = random additive-genetic effect for animal n;  $l_{jlm}$  = random common environmental effect for litter l; and  $e_{ijklmn}$  = random measurement error. For the regression on age at weighing per age class, polynomials of different orders of fit were applied. For age classes 45 and 80 quadratic and for age classes 150 to 650 linear polynomials were used. Higher orders of fit did not achieve a significant influence ( $P < 0.001$ ,  $F$ -statistic, SS Type 1).



Legendre polynomials (LP) for the regression on age at weighing were used for modeling the random effects with RRM. For the orthogonal functions, the age at which the body weight was measured had to be rescaled to a standardized age  $t^*$  using the formula:

$$t^* = \frac{2(t - t_{min})}{t_{max} - t_{min}} - 1,$$

where  $t_{min}$  is the lowest age, here age 30 d, and  $t_{max}$  is the highest age, here age 700 d. The random regression animal model was:

$$y_{ijkl}(t) = \mu + S_i + U_j + Y_k + \sum_{r=1}^3 \beta_r t^r + \sum_{s=1}^S \alpha_{sijkl} \phi_s(t^*) + \sum_{s=1}^S \gamma_{sijkl} \phi_s(t^*) + \sum_{s=1}^S \rho_{sj} \phi_s(t^*) + \varepsilon_{ijkl}$$

where  $y_{ijkl}(t)$  = weight of animal  $l$  at age  $t$  within sex  $i$ , unit  $j$  and birth year  $k$ ;  $\mu$  = population mean;  $S_i$  = fixed effect of sex  $i$ ;  $U_j$  = fixed effect of unit  $j$ ;  $Y_k$  = fixed effect of birth year  $k$ ;  $\beta_r$  = fixed cubic regression coefficient;  $t$  = age in d;  $t^*$  = age standardized to the range -1 to 1;  $\phi_s$  = value of the  $s$ -th LP at standardized age  $t^*$ ;  $\alpha_{sijkl}$  = random regression coefficient for additive genetic effects;  $\gamma_{sijkl}$  = random regression coefficient for permanent environmental effects;  $\rho_{sj}$  = random regression coefficient for common environmental effects within a litter; and  $\varepsilon_{ijkl}$  = random measurement error.

After examining different polynomial structures, the regression of the fixed effects sex, unit and birth year was calculated with a polynomial of second order of fit. The random regression coefficients for additive genetic effect, permanent environmental effect and common litter environmental effect were fitted with LP of second order of fit. The best fitting model was detected by comparing the estimated variances and genetic parameters. It is outlined by Jamrozik and Schaffer (2002) that different test criteria like Akaike's information criterion or the information criterion based on Bayes statistics rank models in a different way. Due to the fact, that it is unclear which criterion is the best for choosing the best fitting model in this study, the model comparison was carried out by using the estimated variances, variance ratios and genetic parameters only (Meyer, 2005).

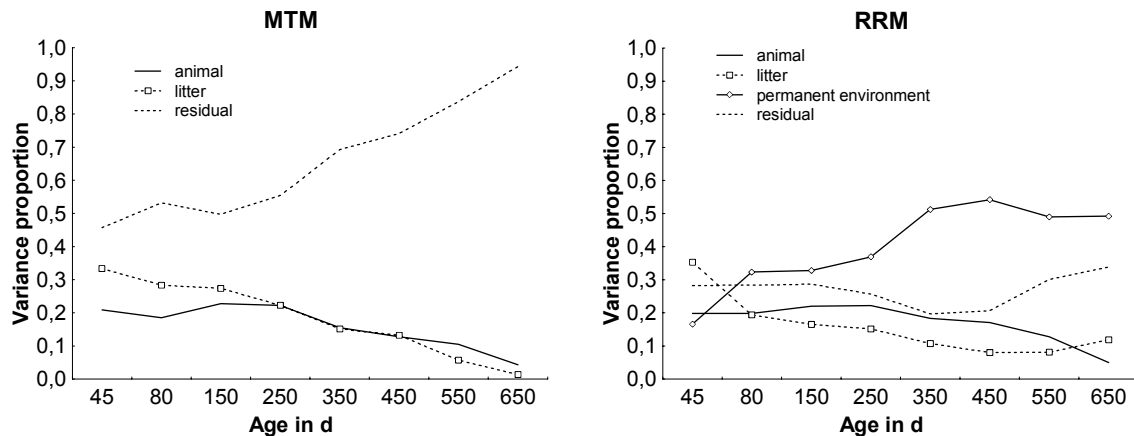
VCE-5 (Kovac et al., 2002) was used to estimate genetic parameters and breeding values for body weight. Eigenfunctions with corresponding eigenvalues were calculated for the covariance components of the random regression coefficients. Eigenvalues represent the amount of variation explained by the corresponding eigenfunction. Accordingly, a large

eigenvalue of the additive genetic effect represents considerable genetic variation for pattern of growth and changes in the growth curve that can be modified by selection (Bermejo et al., 2003).

## Results

As it is shown in Table 1, the number of analyzed records varies just slightly between the first 5 age classes with a maximum of 3,448 records at age 150 d. After age 350 d the number of records in each age class decreased substantially, reaching a minimum at age 650 d with 690 records.

Heritabilities estimated with MTM showed the highest value of 0.228 (0.220, RRM) at age 150 d (Figure 1). The highest value of 0.222 estimated with RRM was calculated for age 250 d (0.223, MTM). After age 250 d, heritabilities estimated with RRM were slightly higher compared to those estimated with MTM.



**Figure 1.** Variance proportions of random and residual effects estimated with MTM and RRM

In Table 2, the heritabilities estimated with MTM and the genetic correlations of MTM and RRM are shown. Standard errors are only provided for estimates of MTM by VCE-5 whereas standard errors for estimates of RRM are not yet available from the used software. All standard errors showed expected values, only in the last age class standard errors for genetic correlations were higher and also the standard error for the heritability was rela-

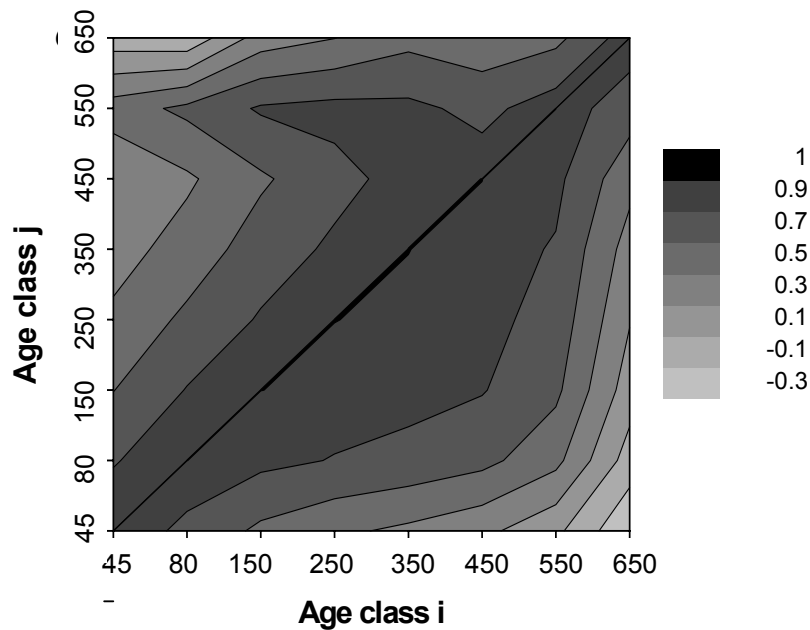
tively higher than in the other age classes due to a lower number of analyzed records in this age class. Additionally, the heritability was much lower at 650 d in both models.

**Table 2.** Heritabilities (diagonal, estimated with multiple trait model) and genetic correlations estimated with multiple trait model (above diagonal) and with random regression model (below diagonal)

Age class	45	80	150	250	350	450	550	650
45	<b>0.209</b> <b>± 0.020</b>	0.889 ± 0.072	0.695 ± 0.059	0.539 ± 0.052	0.420 ± 0.053	0.317 ± 0.051	0.601 ± 0.073	-0.018 ± 0.077
80	0.861	<b>0.185</b> <b>± 0.015</b>	0.909 ± 0.066	0.743 ± 0.059	0.581 ± 0.059	0.468 ± 0.058	0.747 ± 0.081	-0.052 ± 0.080
150	0.658	0.949	<b>0.228</b> <b>± 0.016</b>	0.920 ± 0.066	0.798 ± 0.068	0.670 ± 0.066	0.924 ± 0.090	0.395 ± 0.100
250	0.539	0.891	0.988	<b>0.223</b> <b>± 0.018</b>	0.934 ± 0.082	0.839 ± 0.082	0.959 ± 0.100	0.496 ± 0.121
350	0.457	0.840	0.965	0.993	<b>0.156</b> <b>± 0.016</b>	0.970 ± 0.095	0.945 ± 0.104	0.639 ± 0.142
450	0.353	0.759	0.912	0.960	0.986	<b>0.128</b> <b>± 0.014</b>	0.846 ± 0.102	0.567 ± 0.138
550	0.148	0.557	0.745	0.824	0.883	0.949	<b>0.105</b> <b>± 0.014</b>	0.647 ± 0.158
650	-0.275	0.008	0.200	0.313	0.417	0.561	0.794	<b>0.043</b> <b>± 0.013</b>

The variance proportion of the common litter effect decreased with age in both models (Figure 1). The proportion of the residual variance estimated with MTM showed a constant increase throughout the whole examined time period. The RRM estimated a more or less constant proportion of the residual variance while the variance proportion of the permanent environmental effect increased over the whole time range.

The genetic correlations between body weight measurements in different age classes showed an expected decrease with increasing distance between the age classes (Figure 2). Even negative correlations were estimated between age 45 and ages 80 d and 650 d; however these estimates are based on a very limited number of observations. Correlations estimated with MTM showed unexpected higher values between age 550 d and age 45 to 250 d.



**Figure 2.** Genetic correlations between body weight measurements in different age classes estimated with MTM (above diagonal) and RRM (below diagonal)

The analysis of eigenfunctions and their associated eigenvalues lead to the result that the first eigenfunction with an eigenvalue of 85.55 % had the highest proportion of genetic variation compared to the second and third eigenfunction with 13.98 % and 0.47 %, respectively (results not shown). The first eigenfunction was positive throughout the whole examined time period, which means that a selection on low body weight on the basis of the predicted breeding values at a certain age will change the body weight in the same direction at any age of the trajectory.

### Definition of an operational breeding goal

Goettingen minipigs are sold at a highly variable age (from 30 to > 700 days) for various purposes. For many experimental uses, a lower body weight at the age of use would be economically advantageous. However, the absolute weight reduction (in grams) is not a good indicator across ages, e.g. a reduction of 250 g reflects on average a 4.7 % weight reduction of an 80 d old minipig, while it is only on average a 0.7 % reduction of a 650 d old minipig. In cases where testing compounds are dosed per kg body weight, the weight reduction in % clearly is the appropriate economic indicator, because a weight reduction of

x % will lead to a dose reduction of x %, and the quantity and price of the (often extremely expensive) testing compound will be reduced by the same percentage.

A second aspect to account for in the breeding objective is the proportion of animals sold in the different age classes. Table 3 shows the difference of the number of animals in the different age classes, e.g. in age class 150 we had 2,426 pigs less than in age class 80. We assume, that all these animals were sold (a small proportion may have died, but mortality is negligibly low). Relative to all the observed sales in the considered time window 30 to 700 d, 14.5 % of the sold animals were sold between ages 80 and 150 d. The largest proportion (47.9 %) of animals was sold between ages 150 and 250 d, and almost 20 % are sold when they are older than one year.

**Table 3.** Number and percentage of sold animals per age class and relative weights in % of kg selling weight

Age class	Sold animals	Sold animals (in %)	Relative weight in <i>RWR</i> (in % per kg)
80	0	0	0
150	2,426	14.5	1.7
250	8,012	47.9	3.0
350	3,258	19.5	0.9
450	1,837	11.0	0.4
550	799	4.8	0.2
650	394	2.4	0.1
total	16,726	100.0	

We define the relative weight reduction (*RWR*) as composite breeding objective:

$$RWR_i = - \sum_{j=1}^8 \frac{p_j}{\bar{y}_j} \times a_{ij}$$

where  $RWR_i$  is the relative weight reduction of animal  $i$ ;  $p_j$  is the proportion (in %) of animals sold in time interval  $j$ ;  $\bar{y}_j$  is the average body weight (in kg) in time interval  $j$ ;  $a_{ij}$  is the breeding value of animal  $i$  for body weight (in kg) in time interval  $j$ .

The unit of  $RWR$  is percent, and  $RWR_i = 2.3$  means that animal  $i$  genetically has 2.3 % less body weight in all age classes where these body weights in each age class are weighted with the probability that a minipig is sold at that age. Positive values of  $RWR$  reflect the desired breeding objective, i.e. a weight reduction in the relevant age classes.

Using this definition  $RWR$  is a linear combination of true (or estimated) breeding values in the eight age classes. In Table 3, the relative weights ( $p_j / \bar{y}_j$ ) for all eight weights are given. Predicted breeding values for  $RWR$  were in a range between -18 and +18 % of selling weight from both models. The correlation between  $RWR$  breeding values calculated with parameters obtained from MTM and RRM was 0.94.

### Estimation of expected genetic gain

The expected genetic progress was assessed using selection index theory (Hazel and Lush, 1942) as implemented in the Selection Index Program (SIP) (Wagenaar et al., 1995). The breeding objective was the improvement of  $RWR$ . We compared two scenarios of practical relevance: selection at 80 d and selection at 150 d. At 80 d, less information is available than on 150 d, so the accuracy of breeding value estimation at 80 d is lower. On the other hand, the pool of selection candidates is larger, because 14.5 % of the animals are sold between 80 d and 150 d. There is no difference in generation interval, because both male and female breeders are used first at an age well above 150 d.

From the available data, we analyzed the average amount of information from the selection candidate and its close relatives when the candidate is 80 or 150 d old. Table 4 contains  $r_{TI}$ , the accuracy of breeding values (identical for males and females, because both sexes are selected with the same amount of information), the selection intensities for males ( $i_m$ ) and females ( $i_f$ ), and the male ( $\Delta T_m$ ) and female ( $\Delta T_f$ ) generation interval. Selection intensities and generation intervals were calculated from the available data and averaged over the years. The expected genetic progress per year in the trait  $RWR$  then was calculated as

$$\frac{\Delta G}{a} = \frac{i_m + i_f}{\Delta T_m + \Delta T_f} \times r_{TI} \times \sigma_A$$

where  $\sigma_A$  is the additive genetic standard deviation of trait *RWR*, which was estimated to be 6.69 %.

**Table 4.** Accuracy of estimated breeding values ( $r_{II}$ ), selection intensities for male and female minipigs ( $i_m$ ,  $i_f$ ) and generation intervals for male and female minipigs ( $\Delta T_m$ ,  $\Delta T_f$ ) for the two different selection ages

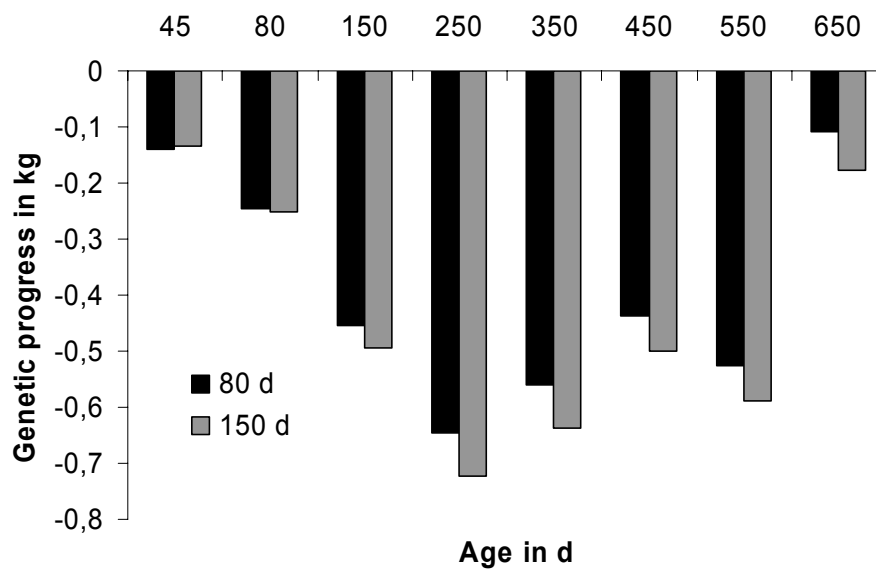
Parameters	Selection age (in d)	
	80	150
$r_{II}$	0.5082	0.5679
$i_m$	2.27	2.24
$i_f$	1.73	1.66
$\Delta T_m$	1.67	1.67
$\Delta T_f$	2.12	2.12

For the calculation of the genetic progress which can be realized per age class and over the whole examined time period, results will be shown only based on genetic parameters estimated with the MTM (RRM-based results were very similar).

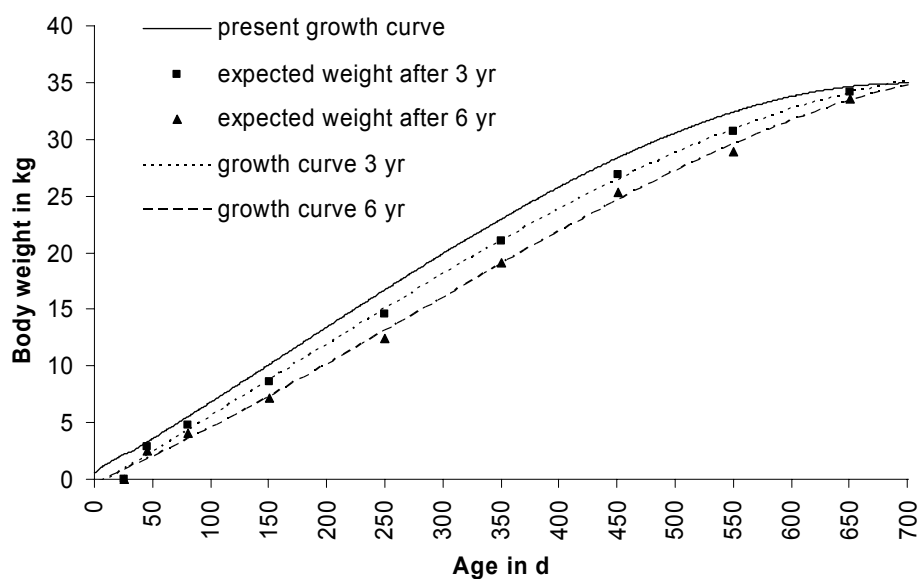
The expected genetic progress in *RWR* was 3.6 % when selection was done at 80 d and 3.9 % when selection was done at 150 d, respectively. Figure 3 shows the expected absolute weight changes in the different age classes whereas the difference between selection at ages 80 and 150 d is more distinct after age class 150. It becomes evident, that selection at 150 d leads to a higher weight reduction throughout all age classes > 45 d, especially in the economically most important age class 250 d (where almost 50 % of all animals are sold) and that the weight reduction through later selection is increased by 12 % (-0.647 vs. -0.724 kg per year). This result is due to the higher accuracy of the estimated breeding values for selection at 150 d, which dominates the slightly reduced selection intensity.

To display the expected changes in the growth curve of the current Goettingen minipig population, body weights from age 0 to 700 d were predicted with the polynomial of third order, which was found to give the best fit for the growth curve in Goettingen minipigs (Köhn et al., 2007b). Expected weight changes in each age class after 3 and 6 years of selection were subtracted from these body weights. Figure 4 shows the current growth

curve and the expected growth curves after 3 and 6 years of selection for body weight reduction, where the resulting values in the eight age classes again were fitted with a third order polynomial. By the suggested breeding scheme and objective the expected change will be a slower weight development in the first year, while the pigs will grow to roughly the same adult body weight during the second year.



**Figure 3.** Expected genetic progress per year for the absolute body weight (in kg) calculated for different selection ages (based on results from MTM)



**Figure 4.** Changes in the current growth curve after 3 and 6 years of selection (based on results from MTM, selection at 150 d)



## Discussion

A breeding scheme for Goettingen minipigs with a focus on the trait *low body weight* is a necessary tool for achieving the customers' demand for a phenotypically small minipig. Genetic parameters were estimated in this study to get the basic results for further application. The estimation was carried out by using MTM and RRM. One aim was to find out which model is the more appropriate one for a routine application in an automatic breeding value estimation and selection with a focus on practicability. Further, the best age for selection had to be identified.

MTM analyses are very common for the estimation of variance components for traits with repeated measurements. The model is able to account for different genetic correlations between the measurements. A problem is the overparameterization of the covariance matrix if measurements at many different ages exist (Meyer and Hill, 1997). Many animals would have missing data for most of the traits if they are randomly measured and not at fixed ages. Thus, a better way is to limit the number of traits by defining time periods (e.g. months) and only take one measurement per time period into account. The disadvantage of this adjustment of age is that the covariance structure is fitted as discontinuous whereas in reality it is continuous. Nowadays, RRM are more and more used for the estimation of genetic parameters of repeatedly measured traits in animals like milk yield or body weight (Albuquerque and Meyer, 2001; Huisman et al., 2002; Lewis and Brotherstone, 2002; Malovrh, 2003). The RRM is able to give the covariances of a trait which is measured at different ages as a function of these ages. There is no need for an adjustment of ages with this model and, as a consequence, errors associated with an adjustment are avoided (Albuquerque and Meyer, 2001).

On the other hand it is outlined by Nobre et al. (2003) that RR analysis requires structured data. Otherwise a bad fit for some curves modeled with RRM may be the consequence. Thus, for the estimation of genetic parameters with RRM on the basis of weight measurements with an uneven distribution as it is given in the original unadjusted data sets with minipig body weights, an adjustment of the results based on estimates from MTM and literature information could be necessary.

The estimation of genetic parameters with RRM of unstructured minipig body weight data failed. A detailed data preparation of every new data set in advance is very labor-intensive and reflects a lack of practicability of the RRM in this specific case. Thus, the MTM seems

to be the more appropriate model for a routine and automatic estimation of breeding values.

The estimated heritabilities were moderate to low in this study. Köhn et al. (2007a) estimated heritabilities with a RRM in the same range for body weight of Goettingen minipigs in a time period of 30 to 400 d of age. A maximum value of 0.25 was estimated at age 225 d. Much higher heritabilities for Goettingen minipig body weight of e.g. 0.77 for age 120 d were estimated by Oldigs (1986). He measured body weight of 204 Goettingen minipigs at 7 different ages including birth weight and estimated the genetic parameters with a sire-dam model. Because of the low number of analyzed records, his results seem to be less trustworthy compared to the results of this study. Malovrh (2003) analyzed body weight measurements of 3,819 boars of 4 German pure-bred lines for fattening pigs. The pigs were weighed six times in an age range from 30 to 167 d. An MTM with six traits and an RRM with animal, litter and permanent environment as random effects were applied. In her study, Malovrh (2003) estimated heritabilities with an MTM also including animal and litter as random effects which were a bit higher than in our study. They ranged from 0.363 at 31 d of age to 0.415 at 145 d of age. Heritabilities estimated with RRM were also higher than in our study and ranged from 0.30 at 31 d of age to 0.40 at 145 d of age.

The changes in variance proportion with decreasing animal and litter effect and increasing permanent environment and residual effects were expected. Up to age 200 d, before the minipigs are used for breeding, a highly standardized environment can be provided. The environmental effects associated to the management practices (e.g. transfer of the sow for mating, transfer of the sow for farrowing) have a bigger influence on the pigs. Thus, the permanent and temporary (residuals) environmental effects increased while the heritability decreased.

The genetic correlations between body weights in different age classes showed an expected decrease with increasing time distance between measurements.

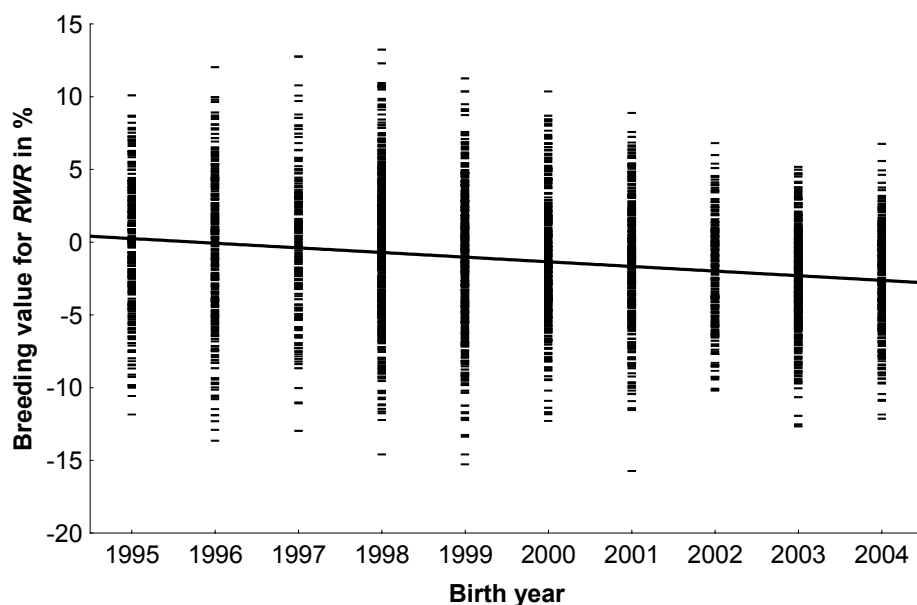
As shown by Köhn et al. (2007b) the Göttingen minipig does not have a sigmoid growth curve, but an almost linear growth curve up to an age of about 500 d, then the growth curve flattens off. While Oldigs (1986) suggested the trait *low adult body weight* as breeding objective, we suggest to use *RWR*, which is an economically weighted average of the proportional reduction of body weight over the relevant age classes. Adult body weight is not a suitable breeding goal, because i) late body weights have a very low heritability (Figure

1), ii) more than 80 % of minipigs are sold with an age less than one year, and iii) using adult body weight would be in conflict with a desired shortening of the generation interval.

In Figure 4, we showed the expected shape of the growth curve after 3 and 6 years of selection for *RWR* based on the suggested selection scheme (using 150 d breeding values). It becomes clear that the main weight reduction is expected at the economically most relevant age at 250 d, while the final weight (adult body weight) remains almost unchanged.

Figure 4 is based on a linear extrapolation of the theoretically derived genetic trend over several years. While this approach is helpful to understand the effects on the growth curve, it must be seen that the Goettingen minipig may be close to a physiological selection limit which may limit the potential to reduce body size by the predicted increment. Therefore, it is necessary to monitor the achieved genetic progress, once the selection scheme is implemented to realize if the expected changes can be achieved.

Body weight is known to have a positive genetic correlation with litter size in pigs (Ferguson et al., 1985). We found a correlation between estimated breeding values for litter size (number of piglets born alive) and *RWR* of -0.197 ( $P < 0.0001$ ), confirming that weight reduction is expected to lead to reduced litter size. Genetic correlations between these traits will be estimated and reported in a separate study. Selection on litter size only in the last ten years caused a negative genetic trend in *RWR* of -0.32 % per year, calculated as the linear regression of birth year on *RWR* (Figure 5).



**Figure 5.** Development of breeding values for *RWR* (in % of selling weight) over the analyzed birth years (based on results from MTM)

Before implementation of a new breeding objective, some aspects need to be discussed given the negative genetic correlation of *RWR* and litter size. A combined objective would be desirable, avoiding the undesired correlated selection response in fertility when selection focuses exclusively on reduction of body weight. Since the absolute economic weights of the different traits can hardly be determined, a possible solution will be to construct a restricted selection index (Kempthorne and Nordskog, 1959) to reduce body weight while keeping litter size constant. Expected cost (in terms of a reduction of genetic progress in *RWR*) will be determined based on the genetic correlations between the trait complexes.

Additional genetic progress could be made if selection intensity was increased and/or generation intervals were minimized. However, since the Goettingen minipig is unique and only exists in four breeding colonies of limited size world wide, avoiding inbreeding and maintaining genetic diversity is an important issue. Effective population size will decrease with increasing selection intensity (Robertson, 1961) and the rate of inbreeding ( $\Delta F$  per year) will increase with a reduction of the generation interval. Therefore, the achievable genetic progress needs to be balanced with an acceptable rate of inbreeding, which can be implemented by using appropriate tools like optimum genetic contribution theory (Meuwissen, 1997).

The results show that a further substantial reduction of the body weight of the Goettingen minipig is achievable. Although some of the practical aspects of breeding and use of experimental animals differ clearly from the situation in slaughter pigs or farm animals in general, the well established animal breeding concepts proved flexible enough to design an efficient breeding program for Goettingen minipigs.

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## **5<sup>th</sup> CHAPTER**

### **General discussion**

## General discussion

This thesis has focused on growth and body weight of Goettingen minipigs. The best fitting function for modeling the growth of Goettingen minipigs from birth up to an age of 700 days was identified and genetic parameters for body weight at different ages were estimated. Further, a breeding scheme was developed by testing different selection strategies to improve the desired trait *low body weight*.

The Goettingen minipig was developed in the 1960's at the University of Goettingen and is exclusively bred as laboratory animal for the use in biomedical studies. It is a miniature breed with normal proportions and is characterized by an adult body weight of 35-45 kg (Bollen et al., 1998), an adequate fertility and a high uniformity within and between the four genetically separated sub-populations. The inbreeding coefficients of the Danish populations which were analyzed in this study are less than 5 % (Bollen and Ellegaard, 1996). Flury (2005) calculated kinship coefficients for the German and the two Danish sub-populations on the basis of a full pedigree. The average coefficients within and between the sub-populations from the animals used in her study are shown in Table 1. At the moment, the breeding goal only focuses on litter size resulting in a slight increase in body weight due to a positive correlation between these two traits (Ferguson et al., 1985).

**Table 1.** Average kinship coefficients within and between three sub-populations of the Goettingen minipig with corresponding standard errors (Flury, 2005).

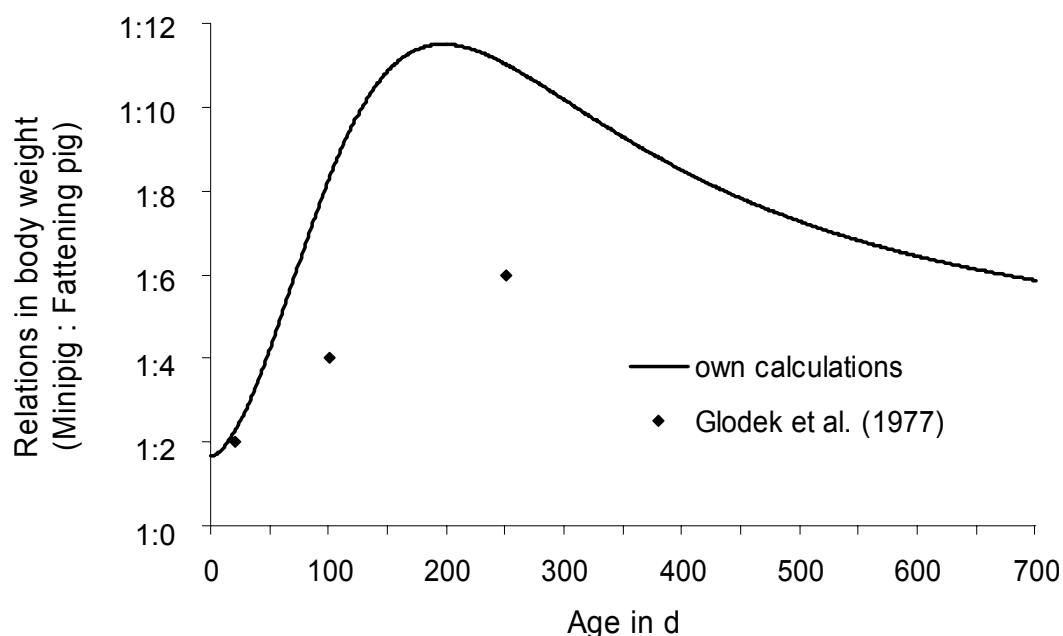
Sub-population	Germany	Denmark 1	Denmark 2
Germany	0.172 ± 0.029	0.148 ± 0.005	0.148 ± 0.003
Denmark 1		0.176 ± 0.031	0.159 ± 0.005
Denmark 2			0.178 ± 0.026

For decreasing the body weight in the minipig populations and improving the genetic progress for the trait *low body weight* firstly the pattern of growth had to be investigated for building an effective breeding scheme in a further step. It has to be noted that the Goettingen minipigs in all populations are fed on a restrictive basis due to a distinct predisposition for high fat content in the body. Thus, the modeled growth curve also represents only growth of restrictively-fed minipigs (chapter 2). Some studies already analyzed the growth and body weight development of Goettingen minipigs but not in this detail for such a big number of animals and records of the present populations (Brandt et al., 1997; Glodek et



al., 1977; Oldigs, 1986). However, the results of these studies are in general in agreement with our results presented in chapter 2.

The growth curve of Goettingen minipigs shows, that the weight development up to an age of around 500 days is approximately linear and then flattens off until the asymptotic body weight is reached (chapter 2). This shape differs in a remarkable way from the growth curve of fattening pigs. Their growth curve shows a sigmoid shape with a slow growth in the first weeks and very high daily gains from around 40 to 160 d of age. Because of the different shapes of minipig and fattening pig growth curve, the differences in body weights between these two breeds at certain ages are increasing with increasing age until the point of inflection of the fattening pig growth curve is reached and the average daily gain is decreasing again. Glodek et al. (1977) calculated relations in body weight of Goettingen minipigs compared to German Landrace for 20, 100 and 250 d of age of 1:2, 1:4 and 1:6, respectively. Own calculations based on body weights estimated with parameters of the Richards function gave relations between body weights of Goettingen minipigs and cross-bred fattening pigs of the German Hybrid Pig Breeding Program of 1:2, 1:8 and 1:11 for the same ages. The relations from own calculations are shown as a curve in Figure 1 whereas the relations of Glodek et al. (1977) are displayed as data points.



**Figure 1.** Relations in body weight of Goettingen minipigs compared to fattening pigs.

The ratios obtained in our own calculations are twice as high for 100 and 250 d of age as those calculated by Glodek et al. (1977). This is due to the fact that fattening pigs used for

our calculations are the result of 30 more years of selection for high daily gain especially in the last two thirds of the fattening period compared to German Landrace pigs used in the study of Glodek et al. (1977). This is also an impressive evidence of the success of selection on average daily gain in fattening pigs in the last decades.

By trying to reach the aim of less body weight it has to be discussed what is the most advantageous change of the growth curve of Goettingen minipigs. One possible change is to decrease the body weight but to leave the shape of the growth curve constant. Thus, the body weight development would remain linear until an age of 500 days but with lower body weights. If the weight development of minipigs is linear especially in their first months, which is the main time period for experimental use, it is much more comfortable for the customers to calculate the right doses and lighter pigs are much better to handle. The breeder has the advantage of an easy reference value for the average weekly gain which should be around 500 g in the first year of life. Additionally, more pigs can be kept in the units because of less required space of smaller pigs. A decrease of body weight without changing the shape of the curve would also result in a lower adult body weight. This is preferable especially for chirurgical tests which are often made with adult minipigs. The minipigs would be smaller and lighter and therefore much better to handle. Also costs for anesthesia or chirurgical tools would be reduced.

Another option for changing the growth curve is to change it more to a sigmoid curve either with or without reduction of the adult body weight. Especially in the first months of their lives minipigs would grow slower. For toxicological tests the minipigs would be even smaller and lighter than in the present population and as a consequence costs for dosing and housing during tests would be reduced in a remarkable way. Depending on the shape of the curve, minipigs would start to grow much faster from a certain age until the stadium of asymptotic weight is reached. If the adult body weight would not be reduced there would be no positive effects for customers who are using adult minipigs. A further disadvantage of this growth curve is the uncertainty of predicting body weight and average weekly gain, mainly in the time period close to the point of inflection. Especially in the first generations under selection when the shape will change, no validated recommendations for feeding and dosing can be made. It therefore seems to be much more practicable to decrease body weight with a constant shape of the growth curve.

As it was shown in chapter 2, there are no differences in growth between male and female minipigs. This result is not in agreement with results from Li et al. (1988) who analyzed

body weight measurements of 539 Goettingen minipigs from the base population in Germany. They found out that females have a higher body weight of 5 to 6 kg with an age of 365 d. Due to the low number of analyzed animals it is expected that the results of Li et al. (1988) were biased because especially with an age of around 365 d many sows were highly pregnant and therefore should not be used to compare body weight between male and female minipigs. In our study, we analyzed body weight measurements of 33,704 animals of the Danish populations. Even though there were highly pregnant sows with body weight measurements the total number of animals adjusts a possible bias of the results. It is therefore concluded, that at the moment no differences in body weights between male and female minipigs exist assuming restricted feeding.

However, it is expected that while selecting on low body weight selected male minipigs of the parental population will have in average a lower body weight compared to selected females of the parental population due to a higher selection intensity of boars (relation between male and female breeders is 1:3).

In chapter 3 and 4 it was shown that heritabilities for body weight in Goettingen minipigs are moderate in a time period of 30 to 700 d. The analysis of eigenfunctions and eigenvalues of the additive-genetic covariance matrix of the random regression model gave the evidence that selection on *low body weight* in this time period is possible. Additionally, it was shown that the genetic correlations between body weights are decreasing with increasing time difference between the body weight measurements. Because of a very low number of records in the last 100 d of the examined time period of 30 to 700 d (chapter 4) it is suggested to focus on a smaller time span as it was done in chapter 3 for 30 to 400 d. Heritabilities were estimated in the same range from data of both time periods. Based on the results from the estimation of genetic parameters and after identifying the best selection age (chapter 4) a breeding scheme with a focus on the traits *low body weight* and *number of piglets born alive (NBA)* can be developed.

Breeding and selection with fattening pigs as the end product is carried out in nucleus herds with a focus on the desired traits. These traits are in pigs usually traits like leanness, average daily gain, carcass quality etc. They are uniform traits for a defined use. The aim of all pig breeders is to maximize the lean meat content with minimized feed intake. That is why breeding schemes for fattening pigs were established to reach this aim. Nowadays, the selection objective for fattening pigs includes genetic merit for leanness, growth rate and feed efficiency (Clutter and Brascamp, 1998). For Goettingen minipigs a breeding

scheme with a focus on low body weight and acceptable litter size has to be developed. The classical selection index theory is used for this purpose (Hazel and Lush, 1942). In this theory, the selection objective is defined as a linear combination of breeding values for all traits of economic importance. The estimates of genetic and phenotypic variances and covariances for the measured traits and the traits in the selection objective and the relative economic importance of the traits in the selection objective are used to build up the optimum index of the phenotypic selection criteria.

For the right choice of the traits in the selection objective in fattening pigs Fowler et al. (1976) proposed to use traits which are based on physiological factors related to the market value of the pig. In fattening pig breeding, the primary product is lean meat and the costs are mainly related to feed efficiency and time. The two physiological traits for the selection objective which Fowler et al. (1976) suggested were *lean tissue growth rate* and *lean tissue feed conversion*.

Concerning minipig breeding, a trait for the selection objective had to be found which expresses the biological trait *low body weight* in a market-relevant way. Therefore, the trait *Relative Weight Reduction (RWR)* was built as it is shown in chapter 4. This trait accounts for the proportion of animals sold at different ages by weighting the breeding values for body weight at a certain age with the probability that a minipig is sold at that age. The proportion of sold animals at a certain age is market-relevant, because every sold minipig increases the profit of the breeder but is on the other hand no longer available for further body weight measurements that would increase the accuracy of breeding value estimation and the genetic progress.

There are several studies which reported a significant direct response to a single-trait selection for weight at a given age in pigs (Kuhlers and Jungst, 1990, 1991a, b). However it has to be noted that body composition of pigs can slightly change after selection for growth and that this change seems to be dependent on the breed. This fact is reported by Kuhlers and Jungst (1991a; 1991b) who selected Duroc and Landrace pigs for high 200-d body weight, observing that these breeds showed opposite reactions on selection. In Duroc pigs carcass fat at 105 kg body weight was increased after four generations of selection for high 200-d weight while in Landrace pigs carcass backfat at 100 kg body weight was decreased and the predicted lean yield was increased significantly after nine generations of selection. Especially in minipigs this circumstance has to be examined after successful selection on low body weight. In this breed meat and carcass traits are not important but

characteristics of organs and blood are in the main focus. All characteristics of the minipig anatomy and physiology are quite well documented concerning hematology, histology, endocrinology and the whole metabolism and medical experiments are adapted to the well documented values of the specific characteristics (Bollen et al., 2006; Ellegaard et al., 1995; Nahas et al., 2002). If changes in these values occur due to selection, they have to be intensively analyzed and reported on an annual basis until stability in these values is reached.

The selection objective of Goettingen minipigs should focus on the two traits *RWR* and *NBA* whereas a combination of these two traits in one selection objective is expected to be problematic due to a positive genetic correlation between litter size and body weight as shown in several studies. While there is no significant influence of selection on high body weight on litter size in the first parity of Yorkshire pigs, positive effects on the following litters are reported (DeNise et al., 1983). A positive effect on litter weight and weaning weight of piglets after selection on high body weight of the sow was also observed by Craig et al. (1956) in Hampshire pigs. In Minnesota minipigs a decrease in litter size by 1 piglet per litter was observed after a 10-year period of selection on low 140-d weight (Dettmers et al., 1971). It therefore seems to be more reasonable to build a restricted selection objective.

In an index with restricted selection, the expected genetic progress of one trait in the selection objective is set to zero while the total rate of genetic improvement in the selection objective is maximized. In the special case of minipig breeding, the genetic progress for the trait *NBA* is set to zero while the genetic progress of the trait *RWR* is still improved. For calculating the restricted selection index minor changes in the formula of the selection index have to be considered (Kempthorne and Nordskog, 1959). Firstly, the selection criterion is determined as if no restriction of the trait *NBA* was done with the traits  $Y_{RWR}$  and  $Y_{NBA}$  in the selection objective. The phenotypic variance-covariance matrix (**P**) of the traits in the selection criterion, the genetic covariance matrix (**G**) between the traits in the selection criterion and the traits in the selection objective and the genetic variance-covariance matrix (**C**) of the two traits in the selection objective are 2 x 2 matrices, whereas **C** is equal to **G** if the traits in the selection criterion and in the selection objective are the same.

An exemplary calculation with a restricted selection index and a ‘normal’ unrestricted selection index was conducted, where the traits in the selection objective were body weight at 150 d of age ( $BW_{150}$ ) and *NBA*. Genetic parameters for the trait  $BW_{150}$  were estimated

with the multiple trait model (chapter 4) and selection intensities for male and female minipigs were calculated on the basis of selection at 150 d of age.

For an unrestricted selection index the matrices **P** and **G** were:

$$\mathbf{P} = \begin{bmatrix} \sigma_p^2(BW_{150}) & \sigma_p(BW_{150}, NBA) \\ \sigma_p(BW_{150}, NBA) & \sigma_p^2(NBA) \end{bmatrix} \text{ and}$$

$$\mathbf{G} = \begin{bmatrix} \sigma_g^2(BW_{150}, BW_{150}) & \sigma_g(BW_{150}, NBA) \\ \sigma_g(NBA, BW_{150}) & \sigma_g^2(NBA, NBA) \end{bmatrix}.$$

The matrices **P** and **G** for the exemplary calculation were:

$$\mathbf{P} = \begin{bmatrix} 2.462 & 0.483 \\ 0.483 & 1.904 \end{bmatrix} \text{ and}$$

$$\mathbf{G} = \begin{bmatrix} 0.561 & 0.081 \\ 0.081 & 0.305 \end{bmatrix}.$$

Economic values for the two traits are given in the vector **w** with two rows. For the unrestricted selection index the economic values were:

$$\mathbf{w} = \begin{bmatrix} w_{BW_{150}} \\ w_{NBA} \end{bmatrix} \rightarrow \mathbf{w} = \begin{bmatrix} 1.10 \\ 0.05 \end{bmatrix}.$$

The selection index weights (b) are  $\mathbf{b} = \mathbf{P}^{-1}\mathbf{G}\mathbf{w}$  and the selection criterion for these two traits was in general:

$$b_{BW_{150}}(Y_{BW_{150}} - \bar{Y}_{BW_{150}}) + b_{NBA}(Y_{NBA} - \bar{Y}_{NBA}),$$

and for the exemplary calculation:

$$0.254(Y_{BW_{150}} - \bar{Y}_{BW_{150}}) + (-0.0095)(Y_{NBA} - \bar{Y}_{NBA}),$$

where  $\bar{Y}_{BW_{150}} = 8.93$  kg and  $\bar{Y}_{NBA} = 6.12$  piglets.

In a second step a new variable  $Y_3$  is introduced to the selection criterion. This results in 3 traits in the selection criterion but still only 2 traits in the selection objective and the calculated matrix **P** is extended by the column of **G** which corresponds to the trait *NBA* (Cameron, 1997) to a 3 x 3 matrix (**P\***):

$$\mathbf{P}^* = \begin{bmatrix} \sigma_p^2(BW_{150}) & \sigma_p(BW_{150}, NBA) & \sigma_g(BW_{150}, NBA) \\ \sigma_p(BW_{150}, NBA) & \sigma_p^2(NBA) & \sigma_g(NBA, NBA) \\ \sigma_g(BW_{150}, NBA) & \sigma_g(NBA, NBA) & 0 \end{bmatrix} = \begin{bmatrix} \mathbf{P} & \mathbf{G}_{NBA} \\ \mathbf{G}_{NBA} & \mathbf{0} \end{bmatrix}.$$

For the exemplary calculation the  $\mathbf{P}^*$  matrix was:

$$\mathbf{P}^* = \begin{bmatrix} 2.462 & 0.483 & 0.081 \\ 0.483 & 1.904 & 0.305 \\ 0.081 & 0.305 & 0 \end{bmatrix}.$$

The  $\mathbf{G}$  matrix also has to be changed whereas just a new row with zeros is added to create a 3 x 2 matrix ( $\mathbf{G}^*$ ):

$$\mathbf{G}^* = \begin{bmatrix} \sigma_g(BW_{150}, BW_{150}) & \sigma_g(BW_{150}, NBA) \\ \sigma_g(NBA, BW_{150}) & \sigma_g(NBA, NBA) \\ 0 & 0 \end{bmatrix}.$$

That leads to the  $\mathbf{G}^*$  matrix:

$$\mathbf{G}^* = \begin{bmatrix} 0.561 & 0.081 \\ 0.081 & 0.305 \\ 0 & 0 \end{bmatrix}.$$

In the vector containing the economic values ( $\mathbf{w}$ ), the economic value for  $Y_{NBA}$  is set to zero after restriction of this trait:

$$\mathbf{w} = \begin{bmatrix} w_{BW_{150}} \\ 0 \end{bmatrix} \rightarrow \mathbf{w} = \begin{bmatrix} 1.10 \\ 0 \end{bmatrix}.$$

Index weights ( $b_{BW_{150}}$ ,  $b_{NBA}$ ,  $b_3$ ) for all three traits are calculated with the extension of trait  $Y_3$ . In a further calculation, the negative index weight of the new variable  $Y_3$  ( $-b_3$ ) is set as economic value for  $Y_{NBA}$  ( $w_{NBA} = -b_3$ ) and the genetic progress is estimated for the restricted selection objective with maximized improvement for  $BW_{150}$  and no genetic change in  $NBA$  (Cameron, 1997). The restricted selection criterion for the example was:

$$0.2303(Y_{BW_{150}} - \bar{Y}_{BW_{150}}) + (-0.0613)(Y_{NBA} - \bar{Y}_{NBA}).$$

The results showed that there are no big differences in the genetic progress ( $\Delta G$ ) for  $BW_{150}$  between restricted ( $\Delta G = -0.362$  kg per year) and unrestricted ( $\Delta G = -0.368$  kg per year)

selection index. Expressed in % for  $RWR_{150}$ , i.e. the genetic progress for  $BW_{150}$  weighted with 0.0168 (chapter 4), the calculated values were -0.608 % per year for the restricted selection index and -0.618 % per year for the unrestricted selection index. This difference in  $RWR_{150}$  of only 0.010 % between the two selection indexes is tolerable and suggests that the restricted selection index can be a good alternative to the ‘normal’ unrestricted selection index. For the trait  $NBA$  the genetic progress in the restricted selection index was set to zero which means that no difference in genetic progress of this trait either positive or negative occurs after selection. Calculated with the unrestricted selection index the genetic progress for the trait  $NBA$  was 0.046 piglets per year. In the case of a body weight reduction this means a reduction in  $NBA$  of 0.046 piglets per year. Due to a low positive genetic correlation of  $r_g = 0.197$  (chapter 4) between the two traits  $RWR$  and  $NBA$  the reduction in  $NBA$  after selection for  $RWR$  is not high but should be considered. The restricted selection index therefore is desirable to assure no reduction in  $NBA$  while keeping the genetic progress for  $RWR$  on an acceptable level.

With this method it is possible to account for the customer’s demand of a smaller pig while the breeder does not have any disadvantages due to a decreasing litter size.

When selecting on a trait one always has to face the circumstance that the calculated genetic progress is usually not in agreement with the real selection response. This can be due to the fact that errors in the estimation occurred and as a consequence the estimated and real population genetic and phenotypic parameters differ in a remarkable way. Further, the selection on one trait reduces both phenotypic and genetic variances in this trait over the generations, an effect which is also known as Bulmer effect (Bulmer, 1971). The prediction of long-term responses of selection based on the response after one generation of selection therefore tends to overestimate the long-term response. When using the estimated heritabilities from an unselected population there will be a substantial reduction of genetic progress after selection due to a reduction of genetic variance. The reduction of genetic variance in the selected parents can be expressed as:

$$V_A^* = (1 - h^2 k) V_A, \quad [1]$$

where  $V_A^*$  is the reduced genetic variance after selection,  $V_A$  is the genetic variance of the unselected population,  $h^2$  is the heritability and  $k$  is the factor by which the phenotypic variance is reduced. Factor  $k$  is calculated as  $k = i(i-x)$ , where  $i$  is the selection intensity and  $x$  is the corresponding deviation of the point of truncation from the population mean



(Falconer and Mackay, 1996). The genetic variance after  $t$  generations of selection depends on the selection intensity in generation  $t$  and  $\Delta\sigma^2$  in generation  $t$ . The  $\Delta\sigma^2$  is the difference between the genetic variance after  $t$  generations of selection and the genetic variance in the unselected population. It is due to genes which are segregating together as a result of selection. For the calculation of genetic variance in the first offspring generation the following formula is used:

$$V_A^* = \left(1 - \frac{1}{2}h^2k\right)V_A \quad [2]$$

The genetic variance in any generation ( $t + 1$ ) can be calculated with the equation (Falconer and Mackay, 1996):

$$V_{A(t+1)}^* = \frac{1}{2}(1 - h_{(t)}^2k)V_{A(t)} + \frac{1}{2}V_A. \quad [3]$$

It has to be noted that the reduction of genetic variance does not continue indefinitely. Its equilibrium value is reached when the increase of the  $\Delta\sigma^2$  due to selection is balanced by the loss due to recombination. Assuming no linked genes the balance is reached after 3 to 4 generations and the genetic progress stays constant until gene frequency changes become large enough to affect it again (Cameron, 1997).

To make this effect more clear Table 2 gives an overview over the reduction in variances and heritabilities for the selected generation of parents and 5 offspring generations compared to the unselected generation. The used variance components for the trait  $BW_{150}$  were estimated with multiple trait model (chapter 4). A selection intensity of  $i = 2$  was chosen with no difference between sexes and a constant selection intensity over the generations was assumed.

The results show the highest difference in variances between the selected and the unselected parental population and a high reduction in variances in the first generation after selection ( $\Delta\sigma^2$ ). Additionally, no differences between generation 4 and 5 were calculated which leads to the conclusion that a constant value in genetic variance is reached after 4 generations.

**Table 2.** Changes in phenotypic and genetic parameters after selection for body weight at 150 d.

Parameters	Parental population		Generation				
	unselected	selected	1	2	3	4	5
i	2.00	2.00	2.00	2.00	2.00	2.00	2.00
x	1.57	1.57	1.57	1.57	1.57	1.57	1.57
k	0.86	0.86	0.86	0.86	0.86	0.86	0.86
$h^2$	0.228	0.228	0.196	0.192	0.190	0.189	0.189
$\sigma^2_P$	2.920	2.51	2.457	2.443	2.438	2.436	2.436
$\sigma^2_A$	0.665	0.535	0.482	0.468	0.463	0.461	0.461
$\Delta\sigma^2$	0	0	0.053	0.067	0.072	0.074	0.074
Formula		[1]	[2]	[3]	[3]	[3]	[3]

In studies which reported selection on *low body weight* in Minnesota minipigs, the problem of differences between predicted and real genetic progress is shown (Dettmers et al., 1965; Dettmers et al., 1971). In their first study, the authors selected Minnesota minipigs for *low body weight* over a time period of 10 years (Dettmers et al., 1965). The estimated heritability for the main selection criterion 140-d weight was 0.41. The predicted genetic progress per year was 2.3 kg, whereas the real genetic progress was only 1.4 kg per year. The authors assume that this difference is due to a decreasing average body weight from generation to generation and a decreasing genetic variance of body weight. Thus, heritability is also decreasing which leads to a lower genetic progress as mentioned above. As another possible reason for the difference between real and predicted genetic progress the authors suggest that also non-genetically small minipigs were selected for breeding (Dettmers et al., 1971). These pigs were only selected due to a retarded growth with no genetic cause. A possible solution which the authors suggest to avoid this problem is to select pigs at a later age when they already express their true body size. Also Lawrence and Fowler (2002) mention the difficulty of detecting animals with retarded growth as a result of inbreeding depression.

Goettingen minipigs are supposed to be selected as early as possible to satisfy the customer's demand of young and light pigs. A selection at a later age would therefore be unfavorable. In chapter 4 it was shown that selection at an age of 150 d leads to the highest

genetic progress of *RWR*. Earlier selection is quite unsure due to low genetic correlations between body weight measurements at early and later ages. It can be assumed that due to high weighing frequencies especially in the first months and a good documentation in the data base and pedigree, non-genetically small pigs can be detected with a high probability and are not used for breeding.

When selecting for *low body weight* or *RWR* a genetic progress in this trait is desired that is as high as possible per year. A possible way to increase the genetic progress is to build a special line with focus on *RWR* with high selection intensities. Another possibility is to cross small pig breeds with the present population of Goettingen minipigs. In other minipig breeds like the Minnesota minipig this was already examined. After establishing the breed in 1949 as a combination of Guinea hog (Alabama), wild boars (Catalina Islands) and Piney Woods (Louisiana) the dwarf pig breed Ras-n-lansa (Guam) was introduced to the population in 1957. Dettmers et al. (1965) analyzed the influence of the dwarf pigs on genetic parameters and weight reduction in the Minnesota minipig population. They calculated a reduction in body weight of 13.6 % for birth weight, 22.7 % for 56-d weight and 28.6 % for 140-d weight after introduction of Guam pigs. Thus, the 140-d weight was reduced from 30.3 kg before the introduction of Guam pigs to 20.3 kg after the introduction. For the 140-d weight which is the main selection criterion the authors estimated heritabilities of 0.21 before the introduction of the dwarf pigs and of 0.41 after the introduction which is due to an increase of additive-genetic variance in the population. Goettingen minipigs have already a low adult body weight of ca. 35-45 kg and a 140-d weight of around 9 kg. Thus, it will be difficult to find a dwarf pig of the species *Sus scrofa* to reduce the body weight in the population.

Different types of dwarfism are known which can be caused by 200 known medical conditions. Most of them are due to mutations in the genome. The most common types of dwarfism in humans are pituitary dwarfism and achondroplasia. The pituitary dwarfism is caused by a growth hormone deficiency (Burns, 1990). The stature is short but the body is proportional. Humans with achondroplasia which is caused by a mutation of the FGFR3 gene (fibroblast growth factor receptor 3) have an abnormal bone growth and a disproportional body (Shiang et al., 1994). Because humans show other irregularities like high blood sugar besides the dwarfism it is expected that also dwarf pigs can have several dysfunctions in their metabolism. It is therefore not advisable to cross Goettingen minipigs with dwarf pigs when the status and the cause of dwarfism are unknown.

A better possibility to reach the aim of a genetically small minipig in the near future may be the use of marker-assisted selection (MAS). Compared to selection only based on BLUP-breeding values a simulated selection based on BLUP and MAS increased the genetic progress by 8-38 % in the first generation (Meuwissen and Goddard, 1996). Pig linkage maps contain nowadays more than 1,000 genetic markers and thus provide a powerful tool for searching quantitative trait loci (QTL) (Wada et al., 2000). Different QTLs for growth-related traits were already identified. QTLs for growth rate were found on chromosome 1, 4, 6, 7, and 13 (Rothschild and Plastow, 1999), whereas the QTL on chromosome 13 for growth rate accounts for 7-12 % of the phenotypic variation. Wada et al. (2000) searched for QTLs in 265 animals of a Meishan pig x Goettingen minipig F<sub>2</sub> cross population with 318 markers. Concerning growth traits the authors found a QTL for birth weight on chromosome 1 which accounted for 14.33 % of the phenotypic variance in the F<sub>2</sub> population and QTLs for average daily gain on chromosomes 9 and 10. The QTL for average daily gain on chromosome 10 explained 17.39 % of the phenotypic variance, the QTL on chromosome 9 explained 10.96 %. Before using MAS in Goettingen minipigs segregating QTLs for growth traits have to be detected in a pure-bred population of Goettingen minipigs. Because the growth measurements and analyzed breeds often differ from one study to the other the detected QTLs do not generally have to be the same. But due to the wide range of published results from other studies the detection of growth-related QTLs in Goettingen minipigs is facilitated considerably. The main advantages of using MAS in the minipig population are a possible pre-selection of breeders only on the marker information and the consideration of markers as additional information in the breeding value estimation to increase the accuracy, resulting in a higher genetic progress. The decision for implementing MAS in the breeding scheme is based on the profitability which is a function of additional genetic progress and costs whereas the potential benefit from MAS is limited by the proportion of the additive-genetic variance that is explained by the QTL. Generally, an increase in genetic progress after implementation of MAS in the breeding scheme by some per cent is expected under good conditions due to a shorter generation interval and/ or an increased accuracy of estimated breeding values.

Each of the four populations of Goettingen minipigs is closed and inbreeding is, besides the present breeding goal litter size, handled with special attention. When building up a new breeding scheme with a combination of the traits *RWR* and *NBA* next to the rate of genetic improvement the rate of inbreeding also has to be taken into account due to the detrimental effects of inbreeding depression. Johnson (1990) analyzed the effect of

inbreeding in reproductive performance traits. The number of total piglets born was decreased by 0.40 when the inbreeding coefficient of the dam was increased by 10 %. For male pigs, the effects of high inbreeding were a reduction in sperm number and libido. For meat and carcass traits, no effect of inbreeding on body composition was reported (Sellier, 1998). In the special case of Goettingen minipigs Brandt and Möllers (1999) reported no significant influence of inbreeding coefficients of sow or piglets on the litter size after analyzing 1,191 litters of 292 sows. However, they found a significant negative influence of higher inbreeding coefficients of both sow and piglets on the birth weight and the growth development of the piglets. Thus, a reduction in birth weight of  $0.7 \sigma_p$  per 10 % increase of the inbreeding coefficient of the sow and a reduction in birth weight of  $0.2 \sigma_p$  per 10 % increase of inbreeding coefficient of the litter were calculated.

It is expected that without controlling the inbreeding coefficient only animals from families with a high genetic merit for *RWR* are selected and therefore, the rate of inbreeding in the next generations is increasing after selection. One method to avoid higher inbreeding in the selected population while improving the genetic progress of the desired trait is to increase the effective population size. A more favorable approach is the predefinition of the acceptable rate of inbreeding for the selected population while maximizing the genetic progress (Meuwissen, 1997). In a first step, Meuwissen (1997) calculates the optimal genetic contributions of male and female selection candidates. In a next step, he restricts the average relationship between the selected animals to reduce the rate of inbreeding in their offspring. When selection of different numbers of males and females is needed like in a minipig population predefined maximum numbers of dams and sires are used. In the study of Meuwissen (1997) it was shown that the predefinition of the parent's coancestry is leading to lower inbreeding coefficients for the following generation, the genetic progress is maximized and the number of selected animals did not increase over the generations.

As it was shown in this thesis Goettingen minipigs have a quite uniform growth (chapter 2) and all important parameters concerning the organs and metabolism are well documented. Breeding for low body weight is favorable especially from an economic point of view, but also has some disadvantages that have to be taken into account. Due to a possibly different size of organs between minipigs and humans after selection for low body weight problems can occur with xenografting. At the moment, Goettingen minipig organs can be used for xenografting studies because of high similarities in organ sizes and weights between minipigs and humans. After successful selection, all organ and metabolism

parameters have to be analyzed for some changes and if changes occur they have to be documented regularly until constant values are reached. Further, although there is a good documentation system, it can always happen that non-genetically small minipigs with retarded growth are selected to inherit low body weight. An additional use of MAS could minimize this problem.

It can be concluded, that for a practicable breeding scheme it seems to be desirable to build up a new line with a focus on selection for low body weight while keeping the litter size constant. How high the proportion of this new line in the whole population should be is dependent on the customer's demand for small and light Goettingen minipigs but it is expected that this line will make the bigger part compared to the line with minipigs of 'normal' body weight. When having two lines, a line with 'normal' minipigs and a line with 'light' minipigs, all claims of the researchers who are using Goettingen minipigs in their studies can be satisfied. For selecting minipigs on the trait *NBA* in the 'normal' line as it is done now it may be favorable to set the trait *RWR* as constant to avoid an increase in body weight in the next generations. With this approach it is possible to breed high quality Goettingen minipigs that qualify for benefit of both breeder and customers.

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