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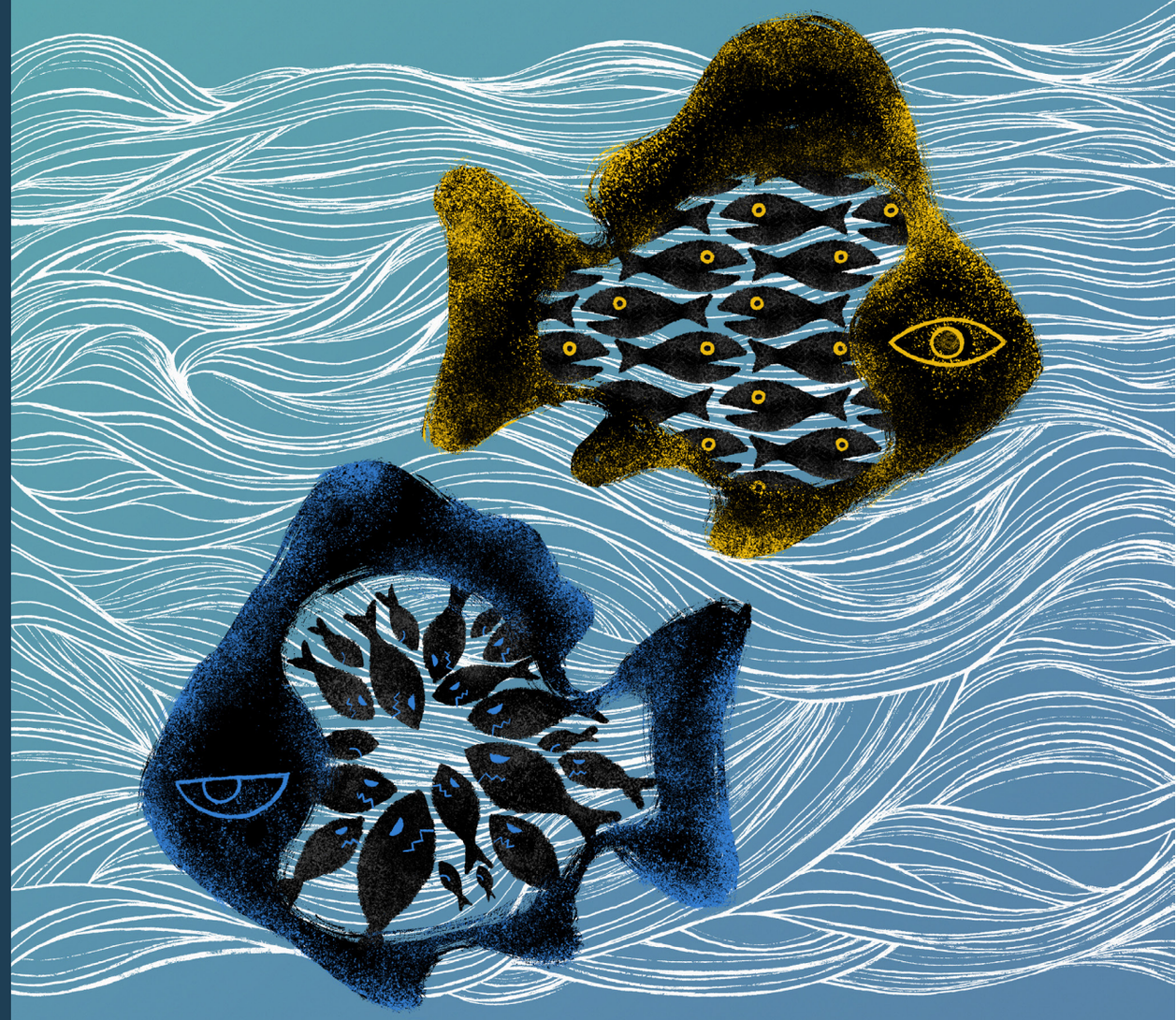
GENETICS OF INHERITED VARIABILITY

Jovana Marjanović

Genetics of inherited variability

INCREASING UNIFORMITY BY REDUCING COMPETITION

JOVANA MARJANOVIĆ



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Genetics of inherited variability

Increasing uniformity by reducing competition

Jovana Marjanović

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Abstract

Social interactions are common for all living organisms. In animal breeding, these interactions are of interest as they are often a source of indirect genetic effects (IGEs). An IGE is a heritable effect of an individual on the trait value of another individual. In aquaculture populations and some plants, social interactions have an additional consequence – interactions in the form of competition inflate variability of trait values among individuals. The phenotypic variability of a genotype has been studied as a quantitative trait in itself, and is often referred to as inherited variability. The main objective of this thesis was to study the genetics of inherited variability, with a focus on the relationship between competition (i.e., IGEs) and variability.

In the thesis, we used Nile tilapia as a model species. We found that variability of body weight and body size traits in Nile tilapia is heritable, and shows a large genetic coefficient of variation, which offers good opportunities for improvement of uniformity by means of genetic selection.

To study the genetic relationship between social interactions and variability, we developed a quantitative genetic model that integrates both phenomena. In this model, interactions between social partners lead to divergence (competition) or convergence (cooperation) of their phenotypes (e.g., body weight) over their life time. The effects of social interaction in the model are heritable and can evolve. These effects comprise direct genetic effect of the focal individual and IGE of its social partner. With a simulation study we showed that the model yields increased variability of body weight with increase of competition, similar to what is observed in real aquaculture populations. Selection for cooperation will therefore lead to decreased variability. These findings suggest that IGEs may be creating an entire level of genetic variation in variability, that has so far been overlooked. Using existing statistical models, we show that direct genetic effects of competition on variability could be captured with a direct model of inherited variability, and similarly, IGEs of competition could be captured with an indirect model of inherited variability.

According to kin selection theory individuals should show better social behavior, i.e., less competition, towards relatives, which should be reflected in their body weight and the variability thereof. We tested this hypothesis by comparing two treatments in an experiment, in which tilapia were reared in either kin or in non-kin groups. Individuals had significantly higher body weight in kin groups, however, there was no difference in variability of body weight between the two treatments.

Findings of this thesis demonstrate that variability of body weight in tilapia is heritable and that genetic variation in variability may comprise not only direct genetic effects but also IGEs. Studies focusing on evolution of variability/uniformity, therefore, should consider IGEs.

Table of Contents

List of publications

This thesis is based on the work contained in the following papers:

I. Marjanovic J, Mulder HA, Khaw HL, Bijma P (2016). Genetic parameters for uniformity of harvest weight and body size traits in the GIFT strain of Nile tilapia. Genet Sel Evol 48: 41.

II. Marjanovic J, Mulder HA, Rönnegård L, Bijma P (in press). Modelling the co-evolution of indirect genetic effects and inherited variability. Heredity. doi: 10.1038/s41437-018-0068-z

III. Marjanovic J, Mulder HA, Rönnegård L, Koning DJ, Bijma P. Capturing indirect genetic effects on phenotypic variability: Competition meets canalization. To be submitted.

IV. Marjanovic J, Mulder HA, Khaw HL, Bijma P. Effects of relatedness between group mates on body weight and variability of body weight in domestic Nile tilapia. To be submitted.

1

General introduction

1.1 Social interactions

Many traits that are important for agriculture are complex quantitative traits. In animal breeding, it is desirable to improve these traits by means of genetic selection. A complete understanding of the potential of a trait to respond to selection requires identifying all sources of genetic variation underlying the trait. Traditional selection methods only consider the direct genetic effects (DGEs) of an individual's own genes on the phenotypic value of the individual. The environmental effects on a trait expression are generally assumed as non-heritable, and therefore not able to evolve by selection. In certain cases, however, the environment itself may have a genetic basis. This alters the genetic architecture and inheritance of a trait.

Animals are social beings who spend the majority of their lifetime engaged in interactions with conspecifics (Allee, 1927). These social interactions are often the most important part of the environment that individuals experience (Wolf, 2003; Frank, 2007). The environment created by social partners through actions such as competition or cooperation, is referred to as the social environment. Variation in the quality of the social environment can be attributed to traits expressed by social partners. Since these traits may reflect genetic variation, the socially provided environment can be heritable (Wolf *et al*., 1998; Bleakley and Brodie IV, 2009). The most extensively studied example of heritable environmental effects is the environment provided by a mother to her offspring (Dickerson, 1947; Willham, 1963; Falconer, 1965; Kirkpatrick and Lande, 1989; Cheverud, 2003; Bijma, 2011).

When the environment contains a genetic component, the phenotype of an individual may not only be influenced by its own genes (DGEs), but also by genes of its social partners. This heritable effect of a social partner on trait values of the focal individual is known as an indirect genetic effect (IGE; referred to as associative effects in Griffing, 1967). IGEs give rise to additional genetic (co)variation, which has consequences for trait values and fitness of individuals that interact, and subsequently for the direction and magnitude of response to selection (e.g. Hamilton, 1964; Moore et al., 1997; Wolf *et al*., 1998).

IGEs have been studied in animals (e.g. Ellen et al., 2014), plants (e.g. Mutic and Wolf, 2007; Brotherstone *et al*., 2011), and microorganisms (Crespi, 2001), and both in natural (e.g. Wilson *et al*., 2011) and in domestic populations (e.g. Muir, 1996; Khaw *et al.,* 2016). A number of studies have shown that social interactions can contribute substantially to heritable variation underlying a trait (reviewed by Ellen *et al*., 2014).

For animal breeders, social interactions with negative effect on trait values, health, and welfare, are especially of interest. Such interactions have been well-documented for laying hens, where cannibalistic behavior causes mortality (Muir, 1996; Ellen *et al*., 2008), and for pigs, where competition and tail biting leads to poorer growth and reduced animal welfare (Arango *et al*., 2005; Camerlink *et al*., 2013, 2014; Bergsma *et al*., 2013). In fish species, social interactions such as aggression and competition have been studied for their detrimental effect on growth of the population (medaka, Ruzzante and Doyle, 1991; Atlantic cod, Monsen *et al*., 2008; Nile tilapia, Khaw *et al*., 2016).

In summary, both empirical and theoretical work show that IGEs can considerably contribute to the potential of traits to respond to selection, and therefore need to be included in the genetic analysis of traits affected by social interactions.

1.2 Social interactions and inherited variability

So far, social interactions have been studied mainly in relation to their effects on fitness and trait values of individuals. However, in aquaculture populations, it has been observed that competition for feed and formation of social hierarchy also increases the variation of trait values among individuals (Jobling, 1995; Cutts *et al*., 1998; Hart and Salvanes, 2000). The variability of trait values of a genotype, measured either on the same individual multiple times, or on multiple individuals belonging to the same family, can be studied as a quantitative trait on its own. This phenomenon is often referred to as inherited variability, genetic variation in uniformity, or heritable variation in environmental variance (SanCristobal-Gaudy *et al*., 1998; Mulder *et al*., 2008; Hill and Mulder, 2010). Genetic variation in trait variability suggests that some individuals are less sensitive to small fluctuations in the environment, which allows them to maintain a stable phenotype.

The study of inherited variability has been an integral part of quantitative genetics for more than 70 years (Waddington, 1942), with growing interest in the topic over the last two decades, largely due to the development of methods to estimate genetic variance in variability (SanCristobal-Gaudy *et al*., 1998; Sorensen and Waagepetersen, 2003; Mulder *et al*., 2009; Rönnegård *et al*., 2010) and increasing empirical evidence for a genetic basis of variability in livestock, aquaculture, and laboratory populations (reviewed by Hill and Mulder, 2010). In addition, variability is an important economic trait in animal production, which further stimulated the research in this area.

In aquaculture, uniformity of body weight has recently been identified as one of the most important traits to be improved by selective breeding (Sae-Lim *et al*., 2012; Janssen *et al*., 2017; Omasaki *et al*., 2017). Studies in Atlantic salmon, rainbow trout, and Nile tilapia found a large genetic component in variability of body weight (Janhunen *et al*., 2012; Sonesson *et al*., 2013; Khaw *et al*., 2015; Sae-Lim, *et al*., 2015a; Sae-Lim, *et al*., 2015b; Marjanovic *et al*., 2016).

The relationship between competition and phenotypic variability is not unique for aquaculture, but can also be observed in plants. Plant breeders have successfully improved productivity of crops by selecting, partly unintentionally, less competitive phenotypes, which has resulted in more uniform crops (Donald, 1968; Austin *et al*., 1980; Denison *et al*., 2003).

These observations suggest that phenotypic variability may also be socially affected trait, with IGEs harboring genetic variation in variability that has so far been overlooked.

1.3 Models of IGE and inherited variability

The quantitative genetics of socially-affected traits have been studied in two modelling frameworks: variance component models and trait-based models (McGlothlin and Brodie, 2009; Bijma, 2014).

In variance component models, the phenotype of the focal individual *i* (P_i) who interacts with a single social partner *j*, is the sum of a direct genetic ($A_{D,i}$) and a direct environmental ($E_{D,i}$) component originating from the focal individual, and an indirect genetic ($A_{I,j}$) and an indirect environmental ($E_{I,j}$) component originating from its social partner *j* (Griffing, 1967):

$$P_i = A_{D,i} + E_{D,i} + A_{I,j} + E_{I,j} \quad (1)$$

In this approach, DGEs and IGEs are estimated as random effects using linear mixed models and information on genetic relationships between individuals (Muir, 2005; Bijma, Muir, Ellen, *et al.*, 2007). When all individuals are both donor and recipient of social interactions, each individual has a direct genetic effect $A_{D,i}$, i.e., a direct breeding value expressed in its own phenotype, and an indirect breeding value $A_{I,i}$, expressed in the phenotype of its social partner. The sum of $A_{D,i}$ and $A_{I,i}$, i.e., the total breeding value, represents the total heritable impact of an individual on the population mean trait value, and the genetic unit of interest in the selection of

individuals for socially affected traits (Moore *et al.*, 1997; Bijma, Muir, and Van Arendonk, 2007).

The second type of IGE models, i.e., the trait-based models, define IGEs on the phenotype of the focal individual as a function of trait values of its social partners (Moore *et al.*, 1997; Wolf *et al.*, 1998; Bijma, 2014). For example, the level of aggression displayed by focal individual is often affected by body weight of its social partner (Thornhill, 1984; Smith and Brown, 1986). Therefore, for empirical use of this model, the traits causing the indirect effects need to be identified. If we consider interaction of two individuals, where the target trait and the trait causing the IGE are the same, the trait-based model equals (Moore *et al.*, 1997)

$$P_i = A_i + E_i + \psi P_j \qquad (2)$$

where P_i is the phenotypic value of the focal individual *i*, A_i is the additive genetic effect and E_i the environmental effect originating from the focal individual, while P_j is the phenotypic value of its social partner *j*. The ψ is known as the "interaction coefficient", and it defines the strength of the social interaction. The ψ can take positive or negative value, and is assumed constant in the population.

Both types of IGE models, however, cannot fully make the connection between competition and variability observed in aquaculture and plant populations, since they model phenotypic variance as largely independent of the level of IGEs (for further explanation see General discussion - Chapter 6). In addition, observations from aquaculture suggest that behavior of a fish towards its social partners depends on its size relative to that of its partners. Therefore, to account for the competitive effect of body weight on growth rate in aquaculture, evolution of body weight needs to be modelled over the life of the interacting individuals. Current IGE models, however, are only applied to the final phenotype.

Quantitative genetics of inherited variability is most commonly studied using a class of models which allow for genetic effects on both the phenotypic mean and the environmental or residual variance of a trait. In the classical quantitative genetic model variation in a phenotype is defined as $\sigma_P^2 = \sigma_A^2 + \sigma_E^2$ (Falconer and Mackay, 1996), where σ_A^2 is the additive genetic variance affecting the mean trait value and σ_E^2 is the environmental variance, assumed to be constant for different genotypes. However, when phenotypic variability differs among genotypes, part of that difference may be attributed to genetic variation in environmental variance, i.e. $\sigma_E^2 = A_v + E_v$, where A_v is the breeding value for environmental variance and E_v is

the residual in environmental variance. Models for inherited variability, however, consider variability as a property of the focal individual, affected only by direct genetic effects, while the potential contribution of the social partner is ignored.

In terms of available quantitative genetic models, social interactions and variability are poorly connected. Therefore, there is a need for new models to understand the relationship between competition and variability observed in aquaculture and plants populations, and the potential of inherited variability to respond to selection.

1.4 Aim and outline of the thesis

The observed relationship between social interactions and variability on the phenotypic level (Jobling, 1995; Cutts *et al*., 1998; Hart and Salvanes, 2000; Denison *et al*., 2003) strongly suggests an underlying genetic relationship between the two phenomena, of which very little is known. The main objective of this thesis, therefore, was to study the genetics of inherited variability and possibilities for its genetic improvement, focusing primarily on the relationship between competition and variability.

Research presented in this thesis is a result of collaboration between Wageningen University & Research and Swedish University of Agricultural Sciences, in cooperation with WorldFish. WorldFish provided the data for Chapter 2 and the experimental facilities used to generate data for Chapter 5. Previous collaboration between Wageningen University & Research and WorldFish resulted in a PhD project which aimed to estimate direct and indirect genetic effects on growth rate in Nile tilapia (Khaw, 2015). This thesis builds on that knowledge, but primarily focuses on relationship between social interactions and variability. The large size differences related to competition for feed, together with the desire to reduce these differences by means of genetic selection (Ponzoni *et al*., 2005, 2011; Khaw *et al*., 2016), makes Nile tilapia an ideal species to study the relationship between social interactions and variability. Therefore, Nile tilapia was also used as a model species in this thesis.

In **Chapter 2** we investigate the potential for genetic improvement of inherited variability of harvest weight and body size traits in a domestic Nile tilapia population. We analyzed within-family variance of harvest weight, body length, depth, and width, by applying a double hierarchical generalized linear models (DHGLM) to individual trait values (Rönnegård *et al*., 2010). In addition to quantifying genetic variation in inherited variability of those traits, we also looked into possibilities of

The general discussion, **Chapter 6**, addresses several topics. First, I elaborate on integrating the two fields in quantitative genetics, social interactions and inherited variability. Second, I discuss benefits and downsides of selection for uniformity in domestic and natural populations. Finally, I give perspectives for selection for uniformity, future studies, and possible applications of the model developed in Chapter 3.

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6

General discussion

6.1 Introduction

Social interactions are common in nature and are an important part of the environment experienced by individuals. When individuals interact, their phenotypes may be affected by genes in their social partners. This heritable effect of a social partner on the trait value of the focal individual is known as an indirect genetic effect (IGE) (Griffing, 1967; Moore *et al.*, 1997). IGEs can also be interpreted as a genetic component in the social environment, i.e., the environment created by social partners. In the terms of classical quantitative genetic model, where the trait value of an individual is a function of genetic and environmental effects, $P = G + E$, the *E*-term is partly heritable when IGEs occur (Wolf *et al.*, 1998; Bleakley and Brodie IV, 2009; Bijma, 2014). However, the classical model assumes that the environmental effects are not heritable. Therefore, there was a need to extend the model to incorporate IGEs, which led to development of two modelling frameworks for IGE, variance component models and trait based models.

IGEs may not only affect the mean trait value, but also variation of the trait around its mean. In fish and some plant populations, competition has been shown to increase variability of trait values. In the past two decades, variability has been studied as a genetic trait in its own right. This trait is often referred to as inherited variability or heritable variation in environmental (residual) variance (SanCristobal-Gaudy *et al.*, 1998; Mulder *et al.*, 2007; Hill and Mulder, 2010). As social interactions are often a source of IGEs, the observed relationship between competition and variability on the phenotypic level (Jobling, 1995; Cutts et al., 1998; Hart and Salvanes, 2000; Denison et al., 2003) strongly suggested an underlying genetic relationship between the two phenomena. Here our knowledge, however, is quite limited, because despite the clear phenotypic relationship between competition and variability, inherited variability has not been connected to competition in quantitative genetic model. On the one hand, variance component and trait-based IGE models cannot fully explain the observed relationship between competition and variability. On the other hand, models for inherited variability treat variability as a property of a single individual.

In this thesis we studied genetics of inherited variability, with specific focus on the relationship between variability and competition, and the contribution of IGEs to genetic variation in variability.

In **Chapter 3** we proposed a quantitative genetic model that allows for indirect genetic effects to lead to differences in variability of trait values, similar to observations in real aquaculture and plant populations. Integrating IGE and inherited variability, and reasons why it was necessary to develop a new model, will be the first topic that I will address in this chapter.

In this thesis we studied genetics of inherited variability. In **Chapter 2** we investigated the genetic basis of variability in body weight and size in a domestic Nile tilapia population. **Chapter 3** & **4** focused on the relationship between variability and competition and how to capture genetic effects of competition on variability. In **Chapter 5** we investigated the effect of relatedness on the level of variability. Understanding the genetic basis of variability is important in animal and plant breeding, both from an economic and an animal welfare point of view. Breeding for uniformity is an analogue of the evolution of canalization in natural populations (Waddington, 1942). In evolutionary biology, canalization is studied for its role in phenotypic evolution (Flatt, 2005). Genetic changes in variability, therefore may have an important impact in both domestic and natural populations. Benefits and downsides of such impact will be next topic I will address.

Finally, I will conclude this chapter by giving perspectives for selection for uniformity, discuss the need for future studies, and possible applications of the model developed in **Chapter 3**.

6.2 Social interactions and inherited variability: bringing two worlds together

As mentioned above, traits affected by social interactions can be modelled using two theoretical frameworks, variance component models and trait based models. Both of these frameworks have been developed from maternal effects theory, which describes a special case of indirect genetic effects, where indirect effects of a mother on the phenotypes of offspring have a heritable component (Dickerson, 1947; Willham, 1963; Falconer, 1965; Cheverud, 1984; Kirkpatrick and Lande, 1989).

In the variance component model, the phenotypic value of the focal individual *i* (P_i), who interacts with a single social partner *j*, is a function of a direct genetic effect of the focal individual ($A_{D,i}$), an indirect genetic effect attributed to the social partner ($A_{I,j}$), and a residual (*e*) (Griffing, 1967):

$$P_i = A_{D,i} + A_{I,j} + e \quad (1)$$

In the trait-based model, the indirect genetic effect of the social partner on the trait value of the focal individual is modelled as a function of the trait value of the social partner. If the trait of interest and the trait causing the IGE are the same, the trait-based model (assuming interaction of two individuals) specifies the phenotypic value of the focal individual *i* as a function of the direct genetic effect of *i* (A_i), non-heritable effects of *i* (e_i), and the phenotype of social partner *j* (P_j) multiplied by an interaction coefficient, ψ (Moore *et al.*, 1997):

$$P_i = A_i + e_i + \psi P_j \quad (2)$$

In the original trait-based IGE-model, the ψ is a population parameter that describes the magnitude of IGEs, i.e., the strength of the social interaction, and is considered constant within a population.

The clear distinction between these models gives them certain advantages and disadvantages in the study of IGEs, depending on the research question and available data. For example, in the variance component model, the traits causing the IGEs do not need to be specified. Instead, the social effect is added to the model as a random genetic effect, and the indirect genetic variance is estimated based on genetic relationships in the data. The variance component model, therefore, gives estimates of direct and indirect genetic effects, but does not disclose the mechanism underlying the IGEs. Trait-based models, in contrast, require knowledge of the traits causing the IGE, but in return quantify the mechanism underlying the social interaction.

To understand the observations from aquaculture and plant populations, where competition for resources increases variability, in this thesis we wanted to integrate IGEs and inherited variability into a single model. Considering available IGE models and models for inherited variability for such study, we encountered the following issues :

1) current IGE-models and models for inherited variability cannot fully explain the observed relationship between competition and variability
2) the interaction coefficient ψ in the trait-based IGE model has the same value for all interacting individuals, i.e., it shows no flexibility

3) IGEs are usually applied to a "final" phenotype, whereas the effect of competition accumulates over time.

6.2.1 Modelling the relationship between competition and variability

In this section I will elaborate on issue number one, by showing the connection between the level of IGEs and variability, or the lack thereof, for each model.

In the variance component model (Equation 1), when pairs of interacting individuals are unrelated, phenotypic variance can be decomposed into the variance of direct genetic effects ($\sigma^2_{A_D}$), the variance of indirect genetic effects ($\sigma^2_{A_I}$), and the residual variance (σ^2_e):

$$\sigma^2_P = \sigma^2_{A_D} + \sigma^2_{A_I} + \sigma^2_e \quad (3)$$

From here it becomes clear that phenotypic variance is only affected by the variance of indirect genetic effects in the population, not by their level. This model, therefore, was not adequate for our research question, as observations from real populations show that competition and cooperation, i.e., sign of average level of IGEs, have a very different effect on variability, whereas variance is always positive and only gives insight in the variation of IGEs in the population around the mean. This was also demonstrated in **Chapter 4**, where indirect models for the trait capture only little of the genetic effects of competition on variability.

In the trait-based model, if we assume that P_i and P_j are the same trait, and that both individuals are both donor and recipient of social interaction, i.e., Equation 2 also applies to individual *j*, then the phenotypic variance on the population level can be derived as follows (Moore *et al.*, 1997):

$$P_i = A_i + e_i + \psi\left(A_j + e_j + \psi\, P_i\right) \quad (4)$$

$$(1 - \psi^2)P_i = A_i + e_i + \psi\left(A_j + e_j\right) \quad (5)$$

Solving the equation gives

$$P_i = \frac{A_i + E_i + \psi\,(A_j + E_j)}{1 - \psi^2}; \qquad P_j = \frac{A_j + E_j + \psi\,(A_i + E_i)}{1 - \psi^2} \quad (6)$$

And phenotypic variance equals

$$\sigma_P^2 = \frac{(1+\psi^2)(\sigma_A^2+\sigma_E^2)}{(1-\psi^2)^2} \quad (7)$$

When $|\psi|$=1, the phenotypic values and the phenotypic variance are undefined (Bijma, 2014). Note that Equation 7 gives the phenotypic variance in a population consisting of many interacting pairs of individuals, not the variance within a pair. Equation 7 shows that the level of ψ affects the phenotypic variance, however, the effect is symmetrical for positive and negative values of ψ, due to ψ^2 term in both the numerator and denominator. Figure 1, Panel A, illustrates how phenotypic variance changes with ψ. This differs from observations from real populations, where competition leads to increase of phenotypic variability, while cooperation decreases variability.

Now let us consider the variance within a pair ("group") of two individuals ($\sigma_{P_{wg}}^2$) **in the trait-based model**

$$\sigma_{P_{wg}}^2 = var\left(P - P_{average}\right) = \frac{1}{4}Var\left(P_i - P_j\right) \quad (8)$$

Using Equation 6, we can express $P_i - P_j$ as

$$P_i - P_j = \frac{(1-\psi)(A_i+E_i) - (1-\psi)\left(A_j+E_j\right)}{1-\psi^2} = \frac{(A_i+E_i) - \left(A_j+E_j\right)}{1+\psi} \quad (9)$$

The variance of $P_i - P_j$ in the trait-based model then becomes

$$Var(P_i - P_j) = \frac{2(\sigma_A^2+\sigma_E^2)}{(1+\psi)^2} \quad (10)$$

and the within-group variance equals

$$\sigma_{P_{wg}}^2 = \frac{1}{2}\frac{(\sigma_A^2+\sigma_E^2)}{(1+\psi)^2} \quad (11)$$

The final equation shows that the within-group variance depends on ψ rather than ψ^2, so that positive and negative values of ψ have different effect on within-group

variance, i.e., negative values lead to higher $\sigma^2_{\bar{P}_{wg}}$, and positive to lower $\sigma^2_{\bar{P}_{wg}}$. This is shown in Figure 1, Panel B, where an increase in ψ causes a drop in variability.

The b_{ij} in our model (**Chapter 3**) measures the effect of a difference in body weight between the social partner and the focal individual on the growth rate of the focal individual. The absolute value of b_{ij} reflects the strength of the social interaction, however *b* can have both positive and negative values. Negative *b* indicates competition, positive *b* cooperation, and an increase in *b* an increase of cooperation. An increase in cooperation in our model leads to a decrease in variability on both population and within-group level, as shown in Figure 2 in **Chapter 3**. Deriving expressions for phenotypic and within-group variance for our model is rather challenging, as the phenotype of the focal individual depends on the phenotypes from the previous time point of both social partner and focal individual. Therefore, in this chapter for our model I present the pattern of change of variability as a function of *b* numerically, by using data simulated in **Chapter 4** and fitting model with mean and random group effect to the final phenotype, i.e., phenotype at the last time point, using ASReml 4.1 (Gilmour *et al.*, 2015). This model gives estimates for within-group, between-group, and phenotypic variance, which were estimated for populations where average *b* is -0.05, 0, or +0.05 (Figure 6.1, Panel D-F).

Comparing our model with the trait-based model, we can see that the main difference occurs for the phenotypic variance. The change in within-group variance shows a similar pattern for both models. Since phenotypic variance includes both within- and between-group variance, the observed difference must be related to the latter.

Starting with the expression from Equation 6, the between-group variance for **trait-based model** is derived as follows:

The group average is given by

$$\bar{P} = \frac{P_i + P_j}{2} = \frac{(A_i + E_i + A_j + E_j)(1 + \psi)}{2(1 - \psi^2)} \qquad (12)$$

The between-group variance equals the variance of the group average,

$$\sigma_P^2 = \sigma_{bg}^2 = \frac{\frac{1}{2}(\sigma_A^2 + \sigma_E^2)(1+\psi)^2}{(1-\psi^2)^2} = \frac{\frac{1}{2}(\sigma_A^2 + \sigma_E^2)}{(1-\psi)^2} \quad (13)$$

Plotting σ_{bg}^2 for different values of ψ using Equation 13 shows an increase in between-group variance with an increase of ψ (Figure 1, Panel C). In our model (Figure 1, Panel F), however, we can see the decrease in the between-group variance. In conclusion, the relationship between competition and variability on the within-group level is modelled in a similar way in our model (**Chapter 3**) and the trait-based model. The main difference between the models can be seen on the population level, where the trait-based model shows symmetrical level of variability for positive and negative values of ψ, while our model shows decrease in variability with positive *b*. My expectation is that competition leads to higher variability on both within-group and population level, which has also been noticed for several species of fish (Mccarthy *et al.*, 1992; Jobling, 1995; Ponzoni *et al.*, 2005, 2011). Therefore our model depicts the co-evolution of competition and variability more realistically compared to ordinary trait-based IGE-models.

Finally, I will show that models for inherited variability fail to connect variability and the level of IGE, using the additive model as an example. The phenotypic value of the focal individual *i* in the classical model is a function of direct genetic effect of *i* on the mean ($A_{m,i}$) and direct environmental effect of *i* on the mean (E_i):

$$P_i = A_{m,i} + E_i \quad \text{or} \quad P_i = A_{m,i} + \chi\sigma_{E,i} \quad (14)$$

where χ is a standard normal deviate, χ~N(0,1) for the environmental effect. With genetic variation in environmental variance:

$$\sigma_{E,i}^2 = \sigma_E^2 + A_{v,i} \quad (15)$$

so that

$$P_i = A_{m,i} + \chi\sqrt{\sigma_E^2 + A_{v,i}} \quad (16)$$

where σ_E^2 is the mean environmental variance and $A_{v,i}$ is the direct genetic effect of *i* for environmental (residual) variance. Models for inherited variability, therefore only consider direct genetic effects of the focal individual on its own variability, ignoring a possible contribution of the social partner. We confirmed this observation

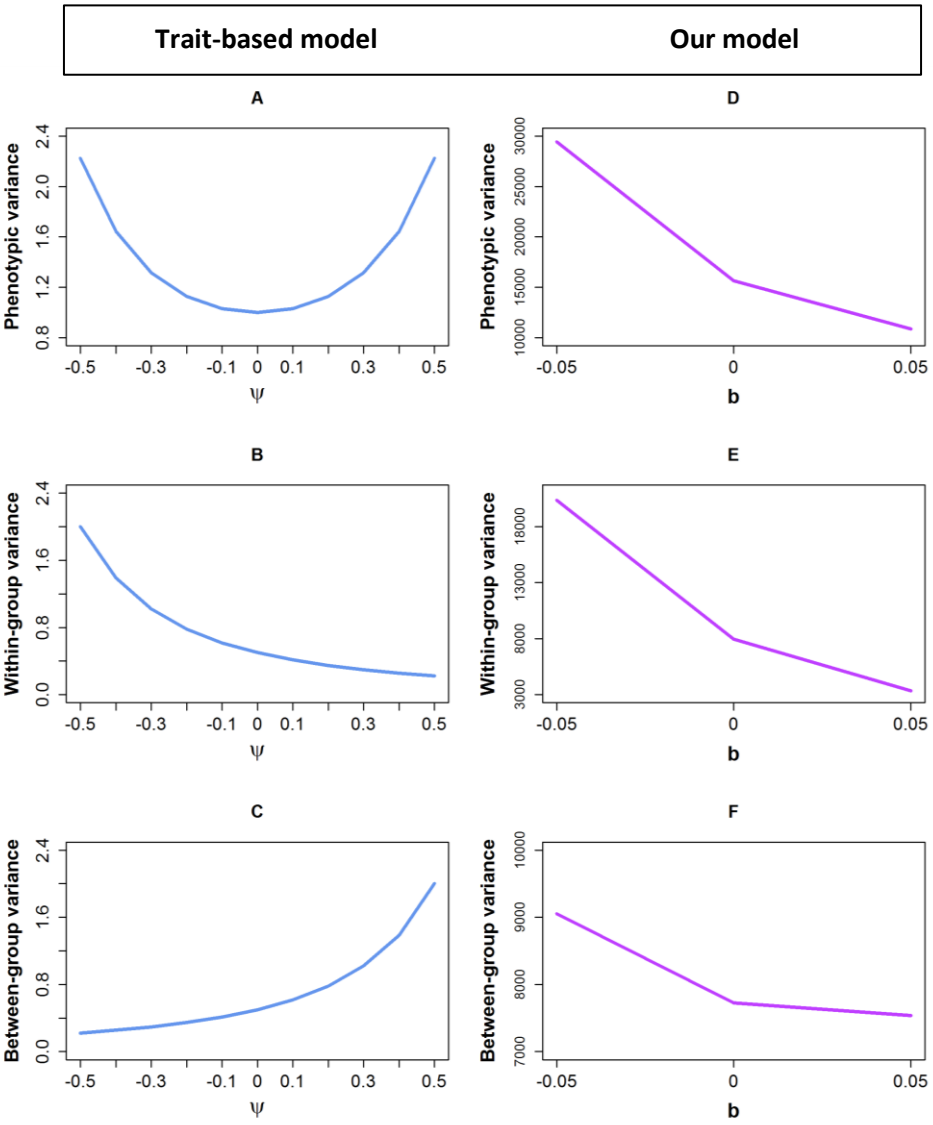

Figure 6.1 Pattern of change in phenotypic, within-group, and between group variance with change in ψ in trait-based model, and change in b in our model. Panels A, B, and C, were made using Equation 7, 11, and 13, receptively, assuming $\sigma_A^2 + \sigma_E^2 = 1$; Panels D, E, and F, were made using estimates from ASReml 4.1, averaged over 10 replicates for each value of b.

in **Chapter 4**, by applying a direct sire model for inherited variability to simulated data. The model captured almost entirely the direct genetic effects of competition (direct breeding values for *b*), but very little of the indirect genetic effect of competition.

6.2.2 Genetic variation in ψ

In the ordinary trait-based model, ψ is assumed to be constant, i.e., to have the same value for all interacting individuals. While done for simplicity, the assumption of constant ψ is rather crude and unrealistic. It is more likely that ψ varies within the population, meaning that ψ itself may respond to selection (Chenoweth *et al.*, 2010). Demonstrating genetic variation in ψ is a challenging task, but can be done, for example, by using multiple discrete genotypes, i.e., inbred lines. Relying on such data, Bleakley and Brodie IV (2009) estimated ψ in guppies and showed that it differs between the focal inbred strains. In addition, the level of ψ in some cases also depended on the social (partner) strain, suggesting that both focal and partner strain contribute to variation in ψ. Similarly, studies on chemical signaling in *D. melanogaster* (Kent *et al.*, 2008) and sexual display traits in *D. serrata* (Chenoweth *et al.*, 2010) also found variation in ψ.

In our study, we wanted to allow variability and competition to co-evolve. For that purpose, the *b* itself needed to be heritable. Inspired by the above-mentioned study on guppies, but also by a study on cannibalistic behavior in laying hens, which shows that such behavior depends on genetic effects of both the social partner (the pecker) and the victim (Ellen *et al.*, 2008), we modelled *b* as a composite quantitative genetic trait. In other words, *b* expresses genetic variation due to direct genetic effects of the focal individual and indirect genetic effects of the social partner. Related to our trait, it means, that the effect of a difference in body weight between the social partner and the focal individual on the growth of the focal individual, depends on genetic competitiveness of the social partner and genetic resistance to competition of the focal individual. Therefore, *b* shows genetic variation and can evolve, which facilitates research on evolution of trait variability due to changes in IGEs.

An additional issue with ψ comes from the feedback effect (Moore *et al.*, 1997; Bijma, 2014). The "feedback" refers to the situation where the "indirect" genetic effects of the focal individual affect its own trait value, indirectly through the social partner. For example, the level of aggression in the focal individual affects the level of aggression in the social partner, which subsequently affects the level of aggression in the focal individual. In those cases, ψ is not a true regression coefficient, because

P and *E* in Equation 2 are correlated (Bijma, 2014). The *b* in our model, however, is a true regression coefficient because the phenotype of the focal individual is affected by phenotype of the social partner from the previous time point, but not vice versa. Therefore, time-series data eliminates the problem of feedback.

6.2.3 Formation of variability

In many species, fitness of an individual depends on its size relative to the size of the other individuals (Smith and Brown, 1986). Fish that are larger often win fights, which allows them to acquire more resources (Huntingford *et al.*, 2012). Because probability of success in a competitive interaction between individuals depends on body size, individuals tend to modify their behavior based on their body size relative to that of social partner. Larger fish, therefore, are usually aggressive, while smaller ones are submissive (Huntingford *et al.*, 2012). In aquaculture, this causes the formation of a social hierarchy, where large fish are at the top of the hierarchy and have priority to feed, while subordinate fish show lower food intake and growth (Vera Cruz and Brown, 2007). As a consequence, dominant individuals show higher and more stable growth, compared to subordinate fish (Mccarthy *et al.*, 1992). Such high discrepancy in growth ultimately leads to increase of variation in body size in time, which has been observed on both group and population level (Jobling, 1995; Ponzoni *et al.*, 2005, 2011).

This brings us to the third issue related to IGE models – as evident from Equation 1 & 2, these models only consider IGEs on the final phenotype. Observations from aquaculture, however, show that variability develops over time. In our model we simulated growth curves in order to incorporate competitive effect of body weight on the growth of focal individuals and mimic the observations from aquaculture population, therefore giving a more realistic impression of how IGEs affect the level of variability. We did, however, for simplicity assume that direct and indirect genetic effects are the same at the different time points, which from biological perspective may not be true, i.e., the level of competition may differ between different stages of fish life.

6.2.4 Other traits

In trait-based models, the indirect effect on the phenotype of the focal individual depends on specific traits of the social partner. Therefore, the traits causing the effect, also known as effector traits, need to be identified. Such information is usually obtained from behavioral studies, and may involve more than one trait. In our model, the effector trait was the difference in body size between the social partner and the

focal individual, which was chosen based on findings in a number of studies on fish behavior (Huntingford *et al.*, 2012). However, other traits may be used as a predictor of variability of body weight instead, or in addition, to the difference in body size. Most likely, these would be traits related to feeding behavior or feed intake and feed efficiency, i.e., traits that affect growth of individual.

In **Chapter 3** & **4** we demonstrated our model using a fish population as an example. However the model may be applicable to other animals, and to plant populations, where a relationship between competition and variability has been observed. In those populations, effector trait(s) may be very different. For example, in domestic pigs variability of body weight can also be related to social hierarchy (Meese and Ewbank, 1973). Several studies suggested initial weight as a key trait for the rank of a certain individual, while higher body weight later in life may not give a competitive advantage (McBride *et al.*, 1964; Meese and Ewbank, 1973). In plants, traits such as height, branching, leaf area, length and branching of the root, determine the competitive ability of an individual (Denison *et al.*, 2003). The difference in level of these traits between social partner and focal individual may be used as an effector traits to investigate relationship between competition and variability. In addition to differences in trait values in plants, distance between interacting individuals would also be needed to take into consideration, as individuals close to each other may exhibit more competitive interactions compared to those that are spaced more distantly.

6.3 Benefits and consequences of selection for uniformity

The main focus of this thesis was on the relationship between competition and variability, which was inspired by observations from aquaculture and plant populations. However, the relationship between these two phenomena may already have existed long before the development of complex organisms and may have played a crucial role in the development of multicellularity.

To understand the evolution of cooperation, scientist often apply game theory, for example a “prisoner’s dilemma” game. According to the prisoner’s dilemma, when two individuals interact, three outcomes are possible: both individuals cooperate; one individual cooperates while other one cheats; both individuals cheat. The scenario where both individuals cooperate brings the highest payoff for both individuals, but that behavior evolves only under certain conditions. Steven A. Frank (2007) gives several examples to demonstrate how mutual cooperation may have

been a key component in the development of multicellular organisms. What I find interesting in these examples is how a high level of cooperation also goes with a high level of uniformity. Slime molds, for instance, live most of the time as single cells, but in certain situations, such as food shortage, they may form aggregations. These aggregates consist of two parts – reproductive cells that form spores, and stalk that raises spores up from the ground. It has been noticed that when these aggregations contain genotypes that are represented more in reproductive part rather than in stalks, i.e., cheating genotypes, the reproductive output of the whole aggregate is decreased because of lower stalk (Frank, 2007). Similarly, if genotypes produce cells in such way that they are equally represented in both parts, success of the whole aggregate is increased. Therefore, in slime molds, mutual cooperation leads to higher uniformity, and vice versa, and higher fitness. These cellular organizations can be considered as predecessors of multicellular organisms (Frank, 2007).

To avoid the possibility of cheating genotypes, multicellular organisms develop from a single-cell, so that all tissue cells are essentially clones. Mutations, however may happen, causing genetic variation and conflict within the tissue. If one of the genotypes has a competitive advantage compared to other, for example, faster cell growth, it may result in severe consequences, such as formation of tumors. Uniformity on the tissue level, therefore, is extremely important. Cell mechanisms such as DNA repair system and apoptotic control evolved to eliminate extreme phenotypes, but in addition genetic and environmental canalization may have had an important role in maintenance of uniformity against small changes in genome and environment (Flatt, 2005). Uniformity, therefore may have relevance for evolution of multicellular organisms and for the stable functioning of such organisms.

In natural populations, uniformity may arise through stabilizing selection for an optimal phenotype (Waddington, 1942; Wagner *et al.*, 1997; Flatt, 2005; Edgell *et al.*, 2009). If the phenotype is at, or near optimum, the variation around optimum is disadvantageous, and an increase in uniformity increases mean fitness of the population. In a study on within-family variance of fledging weight in the great tit, authors found evidence of stabilizing selection on within-family variance (Mulder *et al.*, 2016). In addition, their results show that families with a high or low within-family variance had lower fitness compared to families with an intermediate within-family variance. In some species of fish, uniformity in size, shape, and color, may have evolved through increase of survival of those individuals, as phenotypic similarity between fish that swim together make it difficult for a predator to focus on a single prey, which is known as “confusion effect” (Landeau and Terborgh, 1986). In

conclusion, evolution of uniformity/canalization, is often related to an increase in mean fitness of the population, irrespective of whether such populations consist of single cells or individual organisms.

In domestic populations, uniformity of animal products has a clear economic benefit (Hennessy, 2005). In some cases, an increase in uniformity may also lead to higher survival, for example for litter size in pigs (Sell-Kubiak *et al.*, 2015), and increased welfare, as in aquaculture where uniformity reduces competition and the need for grading (Khaw *et al.*, 2016).

While a reduction of variation may be beneficial, a loss of phenotypic variation may also hinder phenotypic evolution and reduce the ability of a population to adapt to a changing environment (Wagner *et al.*, 1997; Flatt, 2005), which is especially relevant for natural populations. However, while phenotypic variation may be low, the underlying genetic variation may accumulate because it is hidden from the force of natural selection (Wagner *et al.*, 1997; Flatt, 2005). Under extreme environmental conditions, a genotype may become "decanalized", causing more rapid evolution (Flatt, 2005). For example *Drosophila* heat-shock protein Hsp90 buffers genetic variation, unless a stressful environment occurs, such as change in temperature. Buffering ability then becomes compromised and may lead to the expression of new phenotypes (Rutherford and Lindquist, 1998). These results illustrate that phenotypic canalization can go together with the maintenance of heritable variation, so that canalization does not necessarily threaten adaptive potential.

6.4 Future perspectives

Selection for uniformity of body weight in aquaculture could lead to increased profit by producing more fish in the size range that is favored by the consumers, and reducing the need for frequent grading of the fish during the grow-out period, which bares not only financial benefits but also benefits for the welfare of the fish.

Results of theoretical and empirical studies on inherited variability suggest that variability could be reduced by means of genetic selection. However, selection experiments to improve uniformity are scarce, and are mostly limited to laboratory populations (Rendel *et al.*, 1966; Kaufman *et al.*, 1977; Argente *et al.*, 2008; Boldin *et al.*, 2012; Blasco *et al.*, 2017). Findings of **Chapter 2**, together with estimates of genetic variation in variability in several other species of fish (Janhunen *et al.*, 2012; Sonesson *et al.*, 2013; Sae-Lim, Gjerde, *et al.*, 2015; Sae-Lim, Kause, *et al.*, 2015),

suggest that aquaculture populations are suitable to validate the estimated genetic parameters by a selection experiment.

Given the finding of **Chapter 3**, two selection experiments could be performed. A first experiment, where selection is based only on direct genetic effects on variability, and a second experiment where selection involves both direct and indirect genetic effects on variability. These experiments could give us insight into how much of genetic variation in variability could be attributed to variation in IGEs. The experiments should have a group structure with, e.g., two individuals in a group, similar to our simulated data in **Chapter 3** & **4**. However, subsequent trials involving larger group sizes may also be conducted to test whether the magnitude of effects of competition change with an increase of group size. Data on both individuals in each group should be collected at several time points. Time-series data would allow to use random regression approach as suggested in **Chapter 3**, but also the direct model and the indirect model for inherited variability presented in **Chapter 4**. Half sib – full sib designs, similar to that proposed in **Chapter 4**, with multiple observations of within-family variance per sire, and individuals from the same family in both experiments, could be used for estimation of direct and indirect genetic effects of competition. Validation and comparison of the models using real data could make a significant contribution to optimization of methods and models for future studies aiming to estimate genetic effects of competition.

Ideally, these experiments should be performed on aquaculture populations. However, large scale experiments using commercial fish stocks may require considerable investments in finances, facilities, labor, and time. Alternatively, the two proposed selection strategies could be compared by using zebrafish as a model organism. Zebrafish show fast growth and a substantial level of competition, they are small, robust, and easy to maintain. Even though they are not commercial fish, they could elucidate possibilities to improve uniformity in aquaculture, and give an impression of how much IGEs could contribute to the evolution of uniformity. In addition, the genome of the zebrafish has been fully sequenced at high quality, which would facilitate research on genetic and molecular mechanism underlying inherited variability.

One of the main obstacles in incorporating uniformity in aquaculture breeding programs is often high and positive genetic correlation between level and variance of harvest weight, meaning that selection for uniformity will cause decrease in selection response in body weight, which is highly undesirable, especially giving the

low economic value of uniformity (Janssen *et al.*, 2017). It would be interesting to see how indirect genetic effects for *b* correlate with genetic effects for body weight, and whether selection on IGEs only, could be used to improve uniformity, without consequences for growth.

In **Chapter 3** & **4** we suggested approaches to estimate genetic effects of competition, more specifically how direct and indirect genetic effects on *b* could be estimated for each individual. In **Chapter 3** we indicate that random regression could be used to estimate genetic components of *b*, using group-structured population and time series data, while in **Chapter 4** we tested models which are only applied to the final phenotype of individuals within group, therefore avoiding need for multiple observations. Such specific type of data may not be easily available, especially for fish growing in commercial setting. However, with the development of new phenotyping techniques that involve video tracking of individuals in 3D space, generating such data could become common practice (see for example idTracker, http://www.idtracker.es/). These techniques would give multiple observations on individual trait values (for example body weight calculated from the 3D image, i.e., volume of the individual) and information on social interactions between individuals.

In **Chapter 3** & **4** we proposed a model for interaction of two individuals, and discussed how our model could be extended to incorporate IGEs of multiple individuals on the growth of the focal individual. With an increase of group size, IGEs of an individual may show a so-called dilution effect, i.e., decrease in magnitude, due to less time spent in interacting with each of its group mates (Bijma, 2010). Dilution of IGEs does not always happen with increase of group size, for example, alarm signaling in birds will have a similar effect in small and large groups. However, with traits such as growth, where the amount of food is limited, dilution is likely to happen. One main assumption of the dilution effect is that social partner interacts with all group members and in equally intensity, hence IGEs get diluted over a large number of individuals. However for large groups, my expectation is that individuals will interact mostly with small number of same/familiar individuals. This would lead to partitioning of a large group into small sub-groups, so that IGEs might not become heavily diluted. I believe identification of such sub-groups could also be possible with new phenotyping techniques, once they scale up to simultaneously track larger numbers of individuals, which is one of the main future goals of the developers of such technologies.

6.5 Conclusions

To overcome issues of current IGE models and models for inherited variability, integrating social interactions and inherited variability required development of a new model, which was presented in this thesis. The model allows for competition and variability to co-evolve, suggesting that uniformity could be increased through improvement of direct and indirect genetic effects. Estimation of genetic effects of competition requires group-structured data, and also observations from multiple time points in case of estimation with random regression. With development of new phenotyping techniques such data may become commonly available, facilitating application of our model. Ideally, contribution of IGEs to evolution of variability should be quantified in a selection experiment.

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Summary

Summary

Social interactions are common in nature and are an important part of the environment experienced by individuals. In the traditional quantitative genetic model, the phenotype of an individual is determined by the direct effect of its own genes and an environmental effect. With social interactions, however, the phenotype of an individual may also be affected by genes of its social partners. Such effects are known as Indirect Genetic Effects (IGE). IGEs can contribute substantially to heritable variation underlying the trait, and may even reverse the direction of response to selection. A related topic is the inheritance of phenotypic (or residual) variability. The variability of trait values of a genotype, measured either repeatedly on the same individual, or on multiple individuals belonging to the same family, has been studied as a quantitative trait in its own right. This trait is often referred to as inherited variability, heritable variation in environmental variance, or environmental canalization. Results demonstrated substantial genetic variation in variability for many traits. In some species, IGE and inherited variability are related via competition. In aquaculture species and some plants, for example, competition inflates variation of trait values among individuals.

As social interactions are often a source of IGEs, the observed relationship between social interactions and variability on the phenotypic level, strongly suggests an underlying genetic relationship between the two phenomena, of which very little is known. The main objective of this thesis, therefore, was to study the genetics of inherited variability and possibilities for its genetic improvement, focusing primarily on the relationship between competition and variability, and using Nile tilapia as a model species.

In Chapter 2 we investigate the potential for genetic improvement of inherited variability of harvest weight and body size traits in a domestic Nile tilapia population. We analyzed within-family variance of harvest weight, body length, depth, and width, by applying a double hierarchical generalized linear models to individual trait values. Our results showed substantial genetic variation in variability of all analyzed traits, suggesting good prospects for the genetic improvement of uniformity by means of genetic selection. For example, residual variance of harvest weight could be reduced by 58 % with one generation of selection, while proportional change in phenotypic variance would be 36 %. Selection for lower variability of harvest weight in Nile tilapia, however, would come with a consequence on the level of harvest weight, due to high and positive estimated genetic correlation between the two.

Not only direct, but also indirect genetic effects may contribute to genetic variation in variability, as hinted by observations from real populations. In Chapter 3 we make a first step towards understanding the genetic relationship between social interactions and variability, by presenting a quantitative genetic model that integrates both phenomena. In our model, competition between social partners leads to divergence of their phenotypes (e.g., body weight) over their life time. The effects of competition in our model are heritable, and therefore, can evolve. These effects comprise direct genetic effect of the focal individual and indirect genetic effect of its social partner. Simulation results show that our model yields increased variability of body weight with increase of competition, similar to what is observed in real aquaculture populations. Selection for cooperation, i.e., lower competition, will therefore lead to decreased variability. These findings suggest that we may have been overlooking an entire level of genetic variation in variability, the one due to IGEs.

To exploit genetic variation in inherited variability originating from IGEs, we need statistical models to capture this effect. In Chapter 4 we investigate the potential of current statistical models for inherited variability and trait values, to capture the direct and indirect genetic effects of competition on variability. Our results show that a direct model of inherited variability almost entirely captures the direct genetic effect of competition on variability, as illustrated by high correlations between estimated genetic effects and simulated direct breeding values. Similarly, an indirect model of inherited variability captures indirect genetic effects of competition. Models for trait levels, however, capture only little of the genetic effects of competition. Capturing genetic effects of competition, therefore could be possible with direct and indirect models of inherited variability, but may require a two-step analysis.

According to kin selection theory, genetic relatedness should influence social behavior, because individuals able to interact differently with kin *vs.* non-kin would have higher inclusive fitness. In addition to fitness benefits in natural populations, reduced competition may also lead to increased performance in agricultural populations. One potential way to reduce competition and increase yield and uniformity of trait values in Nile tilapia is to utilize the consequences of past kin selection, i.e., the evolution of kin discrimination and cooperative behavior among relatives. In this study we compared two experimental treatments: rearing of fish in kin groups *vs*. rearing in non-kin groups, in order to investigate whether relatedness affects performance traits in domestic Nile tilapia. We analyzed average body

weight, standard deviation and CV of body weight, and survival, between the two treatments. Results of our study show that individuals had significantly higher body weight in groups composed of kin (8.6 ± 2.6 g), indicating that domestic Nile tilapia may exhibit kin-biased behavior. However, there was no difference in variability of body weight and survival between the two treatments.

In Chapter 6, I showed why integrating social interactions and inherited variability required development of a new model, and what are the advantages of the new model, compared to current IGE models and models for inherited variability. The most striking difference between the models comes from modelling of relationship between competition and variability. IGE models and models of inherited variability cannot fully explain this relationship between competition and variability as observed in real population, especially on the population level. Our model, however, allows for indirect genetic effects to lead to differences in variability of trait values, on both group and population level. Furthermore, in this chapter I discussed benefits and consequences of selection for uniformity, and proposed future empirical studies that could give insight into biological relevancy of the theoretical possibility that IGEs contribute to genetic variation in variability.

About the author

About the author

Jovana Marjanović was born on 8th of February 1987 in Bijeljina, Bosnia and Herzegovina. In 2010 she obtained her bachelor degree in Molecular Biology from the University of Novi Sad, Republic of Serbia, with specialization in human physiology. The following year she pursued her master degree in Molecular Biology at the same University, with focus on Molecular Genetics. For her master thesis she studied internal transcribed spacer II (ITSII) and cytochrome oxidase I (COI) as potential barcodes to be used to study phylogenetic relationships among members of the hoverfly genus Merodon (Diptera, Syrphidae), in collaboration with the Finnish Museum of Natural History. After her graduation, in 2013 she was accepted as a PhD candidate in the European Graduate School in Animal Breeding and Genetics program. Her PhD project was a result of a collaboration between Wageningen University & Research and Swedish University of Life Sciences. Jovana had the opportunity to work in both universities, and in addition, in 2016 she has spent one month at WorldFish, in Penang, Malaysia, as a visiting scientist. During her PhD Jovana studied genetics of inherited variability, particularly the relationship between competition and inherited variability. She developed a quantitative genetic model that integrates both phenomena and described possibilities to capture the genetic effects of competition on variability. The results of her research over the course of her PhD are presented in this thesis. In 2017 Jovana started working as a postdoc at Wageningen Livestock Research on the “ReDiverse” project, that aims to increase resilient and competitive use of European Red dairy breeds.

Publication list

Peer reviewed papers

Marjanovic J, Mulder HA, Khaw HL, Bijma P (2016). Genetic parameters for uniformity of harvest weight and body size traits in the GIFT strain of Nile tilapia. *Genet Sel Evol* 48: 41.

Marjanovic J, Mulder HA, Rönnegård L, Bijma P (in press). Modelling the co-evolution of indirect genetic effects and inherited variability. *Heredity*. doi: 10.1038/s41437-018-0068-z.

Khaw HL, Ponzoni RW, Yee HY, Aziz MA bin, Mulder HA, Marjanovic J, *et al.* (2016). Genetic variance for uniformity of harvest weight in Nile tilapia (Oreochromis niloticus). *Aquaculture* 451: 113–120.

Manuscripts in preparation

Marjanovic J, Mulder HA, Rönnegård L, Koning DJ, Bijma P. Capturing indirect genetic effects on phenotypic variability: Competition meets canalization. *To be submitted.*

Marjanovic J, Mulder HA, Khaw HL, Bijma P. Effects of relatedness between group mates on body weight and variability of body weight in domestic Nile tilapia. *To be submitted.*

Conference proceedings

Marjanovic J, Mulder HA, Khaw HL, Bijma P. Genetic parameters for within-family variance of harvest weight in Nile tilapia (Oreochromis niloticus). 10th WCGALP, Vancouver, Canada, 2014, 273.

Marjanovic J, Mulder HA, Khaw HL, Bijma P. Genetic parameters for uniformity of harvest weight in the GIFT strain of Nile tilapia estimated using double hierarchical generalized linear models. ISGA XII, Santiago de Compostela, Spain, 2015.

Marjanovic J, Mulder HA, Khaw HL, Bijma P. Genetic Heterogeneity of Residual Variance in GIFT Nile tilapia. 66th EAAP, Warsaw, Poland, 2015, 21:217.

Marjanovic J, Mulder HA, Bijma P. Modelling the relationship between social interactions and inherited variability. 5th ICQG, Madison, Wisconsin, 2016.

Marjanovic J, Mulder HA, Rönnegård L, Bijma P. Modelling the co-evolution of indirect genetic effects and inherited variability. Gordon Research Seminar and Gordon Research Conference in Quantitative Genetics & Genomics, Galveston, Texas, 2017.

Training and supervision plan

Training and supervision plan

The basic package (7 ECTS)	
EGS-ABG Introduction course, Addis Ababa, Ethiopia	2013
EGS-ABG Summer Research School - Sustainable animal breeding and food security, Addis Ababa, Ethiopia	2013
Research ethics, Uppsala, Sweden	2016
EGS-ABG Fall Research School - Emerging technologies in animal breeding, Wageningen, The Netherlands	2017

Scientific exposure (16 ECTS)	
International conferences	
10th WCGALP, Vancouver, Canada	2014
ISGA XII, Santiago de Compostela, Spain	2015
66th EAAP, Warsaw, Poland	2015
5th ICQG, Madison, USA	2016
Gordon Research Seminar, Galveston, Texas	2017
Gordon Research Conference, Galveston, Texas	2017
Seminars and workshops	
WIAS Science Day, Wageningen, The Netherlands	2014
Workshop Carousel, Wageningen, The Netherlands	2014
WIAS Science Day, Wageningen, The Netherlands	2015
Societal impact, Wageningen, The Netherlands	2015
Aquaculture workshop, Penang, Malaysia	2016
Presentations	
10th WCGALP, Vancouver, Canada, oral	2014
ISGA XII, Santiago de Compostela, Spain, oral	2015
66th EAAP, Warsaw, Poland, oral	2015
5th ICQG, Madison, USA, poster	2016
Gordon Research Seminar, Galveston, Texas, oral	2017
Gordon Research Conference, Galveston, Texas, poster	2017

In-depth studies (19 ECTS)	
Disciplinary and interdisciplinary courses	
Introduction to theory and implementation of genomic selection, Wageningen, the Netherlands	2014
NOVA course - Linear models in animal breeding, Lofoten, Norway	2015
In depth course genotype by environment interaction, uniformity and stability, Wageningen, The Netherlands	2015
Advanced statistics courses	
Advanced statistical and genetical analysis of complex data using ASReml 4, Wageningen, The Netherlands	2014
Modern statistics for the life sciences, Wageningen, the Netherlands	2014
PhD students' discussion groups	
Quantitative genetics discussion group, Wageningen, The Netherlands	2013-2016, 2017
Quantitative genetics study days, Uppsala, Sweden	2016-2017
MSc level courses	
Genetic improvement of livestock, Wageningen, The Netherlands	

Professional Skills Support Courses (3 ECTS)	
Techniques for writing and presenting scientific paper	2015
Presenting with Impact	2015
Career assessment	2017
Data management planning	2017
Reviewing a scientific paper	2017

Research Skills Training (2 ECTS)	
Getting started with ASReml	2014
External training period - SLU, Sweden & WorldFish, Malaysia	2016-2017 & 2016

Didactic Skills Training (5 ECTS)	
Supervising practicals	
Animal breeding and genetics	2014-2015
Supervising theses	
BSc thesis	
Management Skills Training (1 ECTS)	
Organization of seminars and courses	
Aquaculture round table meeting	2015
Education and Training Total	**53 ECTS**

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Colophon

Colophon

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