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Perspective

Indirect Genetic Effects: A Cross-disciplinary Perspective on Empirical Studies

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Abstract

Indirect genetic effects (IGE) occur when an individual's phenotype is influenced by genetic variation in conspecifics. Opportunities for IGE are ubiquitous, and, when present, IGE have profound implications for behavioral, evolutionary, agricultural, and biomedical genetics. Despite their importance, the empirical study of IGE lags behind the development of theory. In large part, this lag can be attributed to the fact that measuring IGE, and deconvoluting them from the direct genetic effects of an individual's own genotype, is subject to many potential pitfalls. In this Perspective, we describe current challenges that empiricists across all disciplines will encounter in measuring and understanding IGE. Using ideas and examples spanning evolutionary, agricultural, and biomedical genetics, we also describe potential solutions to these challenges, focusing on opportunities provided by recent advances in genomic, monitoring, and phenotyping technologies. We hope that this cross-disciplinary assessment will advance the goal of understanding the pervasive effects of conspecific interactions in biology.

Keywords: dynastic effect, genetic nurture, indirect genetic effect, interacting phenotypes, neighbor effect, social genetic effect

I. Introduction

That the traits of individuals are affected by both genes and environment is a truism, but it is less appreciated that an individual's environment includes the genes of other individuals. The papers in this special issue of the *Journal of Heredity*, and the American Genetic Association (AGA) Symposium on which it is based, describe many ways in which consideration of "genes as environment" affects our understanding of fundamental biological processes. Papers in this issue consider interactions between competing species (Girardeau et al., 2022), interactions between mitochondrial and nuclear genomes (Rand et al., 2022), and modifications of the nonsocial environment by interacting conspecifics (Aguillo et al., 2022), as different instantiations of "genes as environment."

Here, we explicitly focus on environmental effects arising from genes of interacting conspecifics. These effects are known as indirect genetic effects (IGE), in contrast with "direct genetic effects" (DGE) arising from the individual's own genotype (Moore et al., 1997; Bijma, 2014). Because all organisms interact with conspecifics during some part of their life cycle, the opportunities for IGE to influence Darwinian fitness and phenotypes are ubiquitous. Indeed, the concept of IGE has been modeled and explored experimentally by agricultural and evolutionary biologists, ecologists, biomedical geneticists, and social psychologists (Table 1). Several papers in this Special Issue describe exciting new theoretical and empirical work on IGE (Fitzpatrick and Wade, 2022; McGlothlin et al., 2022; McGlothlin and Fisher, 2022; Wade, 2022; Walsh et al., 2022).

Table 1. The vocabulary of indirect genetic effects

Field	Term	Key papers
Agricultural Genetics	Indirect genetic effect; social genetic effect	Ellen et al. (2014)
Behavioral Ecology	Indirect genetic effect; interacting phenotypes	Bailey et al. (2018)
Biomedical Genetics	Genetic nurture; dynastic effect; indirect genetic effect; social genetic effect; horizontal effect	Young et al. (2019)
Evolutionary Biology	Indirect genetic effect; interacting phenotypes; maternal genetic effect; GxG epistasis	Wolf et al. (1998)
Population and Community Ecology	Associational effect; neighbor effect	Underwood et al. (2014)
Social Psychology	Social niche construction; evocative rGE	Mills and Tropf (2020)

In this Perspective, we provide a brief history of the development of the IGE concept in different disciplines. We then focus on the many challenges faced by empiricists seeking to understand the influence of IGE on phenotypes, and on potential solutions to these challenges. Our focus is on empirical issues because 1) we ourselves are empiricists and 2) in most arenas, the mathematical development of IGE theory has outpaced empirical understanding.

A Brief History of IGE

To our knowledge, the concept now known as IGE was first introduced by agricultural biologists who noticed that artificial selection on heritable traits did not always yield the expected results. For example, genotypes of crops that had the highest yield in mixed stands had the lowest yields in genetically pure stands (Wiebe, 1963). Notably, Dickerson (1947), Willham (1963), and Griffing (1967) extended traditional models of quantitative trait variation to include both the effects of an individual's own genotype and the effects of genetic variation in conspecifics. In Dickerson's and Willham's models, the conspecific individuals were mothers, and the effects they described are now known as maternal genetic effects. Griffing's model assumed that genetic variance in an individual's phenotype could be affected by genes expressed in unrelated, but interacting, conspecifics, which he termed "associate effects." These models did not specify the phenotypic traits of interacting partners that caused the associate effects. Instead, the total phenotypic variance in the focal trait was partitioned into a direct component attributable to an individual's own genotype and an indirect component attributable to the genotypes of the individual's "associates."

Experimental work by agricultural and model organism geneticists used these "variance-component" models to explore the role of maternal genetic effects (reviewed by Cheverud, 1984) and associate effects (e.g., Wright, 1985; Muir, 1996; Muir, 2005), on the response to selection. As more general statistical approaches became available (e.g., mixed models that allow empiricists to use information on multiple types of relatives simultaneously, or "animal models"; Henderson, 1953), they allowed IGE to be estimated in a great variety of systems, including free-living populations of plants and animals (Wilson et al., 2011; Moiron et al., 2020), outbred populations of laboratory organisms (Baud et al., 2017), and humans (Xia et al., 2021). These approaches have also been extended to map the individual loci giving rise to IGE (Mutic and Wolf, 2007; Bailey and Hoskins, 2014; Ashbrook et al., 2015; Brinker et al., 2018; Baud et al., 2021).

Beginning late in the 20th century, evolutionary biologists developed models in which IGE were attributed to specific traits expressed in interacting partners. The first of these "trait-based" IGE models (Moore et al., 1997) built upon a maternal-effects framework developed by Falconer (1965) and Kirkpatrick and Lande (1989). These models specify the traits in interacting individuals that influence the focal individual's phenotype, defining an "interaction coefficient" Ψ that quantifies this influence. These models have therefore been called "interacting phenotype" models. Formally, Ψ is a path coefficient that describes the degree to which trait X in an interacting conspecific affects trait Y in the focal individual. Critically, the genetic basis of the traits involved are captured in other parameters of these models, specifically parameters that describe genetic variances and covariances of the interacting phenotypes. Thus, while the term "indirect genetic effect" was first used in the context of the trait-based approach, the parameter most identified with that approach, Ψ, does not, by itself, capture the genetic effect of partners on the focal phenotype. Nevertheless, the trait-based theoretical framework describes important implications of IGE for understanding and predicting the evolution of phenotypes (Moore et al., 1997; Wolf et al., 1999; McGlothlin et al., 2010). Given these implications, it is surprising that empirical applications of these predictive models are comparatively rare, although examples are accumulating (see Brodie (2022), McAdam et al. (2022), and Bailey and Desjonquères (2022) in this issue for further discussion). We provide more details about the uses and relationships between variance-component and trait-based approaches in Box 1.

In the 2000s, human behavioral geneticists used structural equation models and extended twin designs to investigate the contributions of assortative mating (nonrandom mate choice) and marital interactions (influence) to phenotypic variance (Agrawal et al., 2006; Grant et al., 2007). More recently, structural equation models have been applied to datasets of unrelated individuals to quantify and map parental IGE on body weight using effect sizes from genome-wide association studies (GWAS) of own and offspring phenotypes (Warrington et al., 2019; Wu et al., 2021). Structural equation models in human IGE studies primarily model effects arising from the *genotypes* of partners, much like variance-component models do, but in some cases they have been extended to test whether specific *phenotypes* of partners mediate the detected IGE (Warrington et al., 2019), a question that is addressed with trait-based models in other disciplines.

Finally, in the last few years, human genetics studies have adopted another approach to study IGE: polygenic scores (also called polygenic risk scores). Polygenic scores are constructed by combining individual genotypes with effect sizes obtained from a previously-conducted GWAS for a particular trait to predict individual phenotypes (Wray et al., 2007). For example, To detect parental IGE on offspring in an Icelandic cohort, Kong et al. (2018) first calculated

Box 1. Variance-component and trait-based models and other approaches

While both variance-component and trait-based approaches can, in theory, be applied to understanding the genotype–phenotype relationship across a wide variety of scenarios, different disciplines have preferred one or the other approach. Overall, variance-component models have been used in many more empirical studies than trait-based models. These differences derive both from the goals of the studies and from practical considerations.

Agricultural genetics is aimed at stock improvement, a pursuit that often does not require knowing which traits in interacting partners mediate IGE, making variance-component models sufficient to achieve this goal. For example, the phenotypes that determine crop competitive ability can be cryptic, but Griffing (1976) was able to conclude that family-based selection could overcome constraints on the response to individual selection that occurs when good competitors reduce performance of their neighbors. By contrast, evolutionary biologists and behavioral ecologists are often interested in traits that mediate interactions between social partners, some of which are difficult to define without reference to traits in other individuals (e.g., social dominance; Moore et al., 2002; Wilson et al., 2011), making trait-based approaches better suited in these disciplines.

Practical considerations have favored variance-component models over trait-based models in empirical studies. First, given the complexity of social interactions, a priori knowledge of mediating mechanisms is often absent, precluding the use of trait-based models. As variance-component models do not require specifying the traits of partners eliciting IGE, they can be applied to a broader range of traits (in fact, *any* trait), provided a pedigree or the genotypes of partners are available; (Bijma, 2014; Baud et al., 2017). Second, while the interaction coefficient Ψ is straightforwardly estimated as a partial regression coefficient in the absence of feedback or with a correction in the presence of feedback when the partner trait is the same as the focal trait (Bijma, 2014), estimating the matrix of Ψ when multiple phenotypes are interacting with feedback is only possible with repeated measures (Martin and Jaeggi, 2021). In addition, Ψ estimates calculated from observed phenotypes are only valid under the assumptions that all causally interacting phenotypes have been identified (Bijma, 2014). When repeated measures are available, however, it is possible to account for unmeasured effects to obtain unbiased estimates of Ψ (Martin and Jaeggi, 2021). Finally, estimates of Ψ are usually not sufficient to quantify IGE and predict the response to selection; genetic variances and covariances of the focal and the interacting phenotype also need to be estimated (Moore et al., 1997; Martin and Jaeggi, 2021). As an alternative to estimating genetic parameters, however, behavioral ecologists often deploy the "phenotypic gambit" (see Box 1 in Dingemanse and Araya-Ajoy, 2015). Laboratory experimentalists, on the other hand, have used inbred strains to ensure Ψ reflects social effects of genetic origin rather than social environmental effects (Bleakley and Brodie, 2009).

There is increasing work to reconcile the variance-component and trait-based frameworks and to overcome their respective limitations. In particular, McGlothlin and Brodie (2009) showed that the 2 frameworks are mathematically equivalent—assuming all interacting phenotypes have been identified in the trait-based models—and developed methods to calculate Ψ from variance components. To date there have been few, if any, subsequent attempts to apply these techniques, however. The polygenic scores used in human genetics (Kong et al., 2018) constitute a hybrid approach. They are trait based—in that a specific trait of partners is investigated—but also inherently genetic in that polygenic scores of partners are used instead of their phenotypes. While this approach is appealing for gaining the benefits of both variance-component and trait-based approaches, we note that the human GWAS used to calculate polygenic scores typically include tens to hundreds of thousands of individuals, sample sizes that are currently achievable in very few other species.

parental polygenic scores for educational attainment and other traits by combining the nontransmitted alleles of parents with effect sizes from a previous GWAS conducted on 279 000 unrelated individuals, then tested for associations between parental polygenic scores and offspring traits. This approach highlighted the role of "genetic nurture"—parental IGE mediated by traits genetically correlated with educational attainment. Polygenic scores have since been used to investigate a wider range of IGE, including between spouses (e.g., Clarke et al., 2019) and schoolmates (see, e.g., Sotoudeh et al., 2019). This approach is trait-based—it requires focusing on a specific trait of parents—but the trait value of parents is predicted from genomic data instead of being measured directly as in classical trait-based approaches.

Whatever approach is taken, the importance of IGE is increasingly appreciated across many subfields of genetics, and attempts to identify and quantify IGE are accelerating. This substantial overlap across disciplines can easily be overlooked, however, because different disciplines use different language to describe conspecific-induced components of the phenotype. A cross-disciplinary synthesis of IGE therefore requires a synthesis of the language used to describe IGE. In Table 1, we present vocabulary used to describe IGE in different subfields. We do not attempt to provide a comprehensive list of citations, since the list would be very long. However, we cite a key primary paper or review for each subfield.

Consequences of IGE (or "So What?")

Across the disciplines listed in Table 1, researchers recognize that the consequences of genes-as-environment can be profound. Evolutionary and agricultural biologists have shown that, when phenotypes are influenced by both DGE and IGE, response to natural or artificial selection can be either greatly accelerated or highly constrained, depending on the nature of the interaction (Wolf et al., 1998; Bijma and Wade, 2008; Peeters et al., 2012). For example, mussels genetically predisposed to grow quickly are also genetically predisposed to reduce growth in their conspecific neighbors via food competition (Brichette et al., 2001). This kind of negative correlation between IGE and DGE, which has also been documented in other species (Wolf, 2003; Santostefano et al., 2017; Thomson et al., 2017), can prevent populations from responding to selection, or cause the response to be opposite in direction to that expected based

on traditional measures of genetic variance and heritability (Moore et al., 1997). Conversely, a positive correlation between IGE and DGE can dramatically accelerate response to selection. For instance, *Peromyscus* mice that are genetically liable to be aggressive also induce high levels of aggression in their social partners (Wilson et al., 2009). Selection favoring increased aggression will therefore increase the frequency of alleles with DGE for high aggression, which will also produce a more aggressive social environment via IGE. This positive feedback between DGE and IGE amplifies the evolutionary change that is expected based on DGE alone. Indeed, the potential for this kind of feedback in social interactions has been proposed to explain the high phenotypic variation and rapid evolution often observed in behavioral and social traits (Reale et al., 2007; Bailey et al., 2018).

When, in addition to traits being influenced by DGE and IGE, the 2 kinds of effects interact (i.e., IGE depend on the genotype of the focal individual), the resulting interaction has been called "GxG epistasis" (Wolf, 2000; Jaffe et al., 2020). This DGE x IGE interaction is of particular interest to evolutionary geneticists because it can promote the maintenance of genetic and phenotypic diversity, as was recently found in color-polymorphic mosquitofish (Culumber et al., 2018). There, juveniles achieved better body condition when their own genotype was rare in the social environment, suggesting that within-genotype competition generates negative frequency-dependent selection and contributes to the maintenance of polymorphism. The examples in this and the previous paragraph, and many others, illustrate that the evolution of phenotypes cannot be fully understood or predicted without accounting for IGE.

IGE also have profound effects beyond determining response to selection and maintenance of genetic variation. Failing to properly account for IGE can bias estimates of DGE and heritability (Bijma, 2014; Baud et al., 2017; Young et al., 2018). Indeed, IGE can account for at least part of the "missing heritability" documented for traits like human height and can influence our understanding of traits with important societal implications such as educational attainment (Young, 2019). Similarly, IGE can bias polygenic scores, which estimate an individual's genetic propensity for a trait or disease and which have been used as a tool both to understand the shared genetic etiology between traits and for precision medicine. Human geneticists would like to use polygenic scores to reflect only the causal effects of an individual's own genes, that is, DGE. However, familial IGE bias these scores (Kong et al., 2018; Trejo and Domingue, 2018; Young et al., 2019; Balbona et al., 2021). The growing awareness of the need to distinguish familial IGE from DGE in human genetics emphasizes the importance of collecting genomic and phenotypic data within families (Young et al., 2019).

As recognition of the importance of IGE increases across disciplines, empirical challenges to estimating and mapping IGE should not be ignored. In the remainder of this Perspective, we describe some of these challenges (Part II), highlight exciting potential solutions (Part III), and conclude with recommendations, drawn from work in many different disciplines, that will advance empirical understanding of IGE (Part IV). We note, however, that this is a small subset of the compelling themes that were discussed at the 2021 AGA President's Symposium on Genes as Environment, and that many of these are described in the papers that form this Special Issue. We also point to an informal compilation of speaker's perspectives published on the AGA website (http://blog.theaga.org/presidential-symposium-contributors-speak-on-the-present-and-future-of-indirect-genetic-effects/).

II. Challenges for Empirical Studies of IGE

In this section, we describe what are, in our view, some widespread challenges to the empirical study of IGE across the disciplines that use the concept. These challenges mainly involve problems of *identification* (e.g., of interacting partners, of changes in partners, or of interactions over time) and problems of *confounding* (e.g., arising from nonrandom group formation, shared environmental effects, relatedness, and population structure). We also describe which of these challenges are general to quantitative genetic analyses, and which arise specifically in the study of IGE.

Identifying Interacting Partners

To understand how traits are influenced by interactions with conspecific individuals, it is of course necessary to identify the relevant partners. While this is straightforward in experimental settings where groups are formed by the experimenter, it can be quite challenging in free-living populations. In free-living animals, identifying interacting partners typically requires time-intensive observations of social interactions (Altmann, 1974), the ability to easily identify individuals in a population (either using distinctive natural markings or by capturing and tagging individuals), and/or the ability to locate nests/dens or to genotype individuals to assess parentage. Even in sessile organisms, it is necessary to know which individuals within populations interact with one another and which do not. That is, the spatial scale over which relevant interactions occur is not always obvious (File et al., 2012; Brodie, 2022; McAdam et al., 2022).

Dealing With Nonrandom Group Formation

Most interactions with conspecifics do not occur at random with respect to the genotypes, environments, and phenotypes of the individuals involved. For example, in many species, individuals interact preferentially with kin, resulting in correlations between the genotypes, environments, and phenotypes of group members. Similar correlations can also arise as a result of population structure, since interactions then occur most frequently genetically-similar individuals or individuals sharing a similar environment. In free-living organisms, population structure can arise passively from migration–selection–drift processes (Wright, 1978) or from genetically based habitat preferences (D'Aguillo et al., 2019). Finally, correlations between group members can arise when individuals actively choose their partners based on their own and potential partners' phenotypes (e.g., Robinson et al., 2017; Aguillo et al., 2022; Brodie, 2022).

When groups are not formed at random, IGE can be defined in 2 alternative ways. IGE are most commonly defined to reflect the *influence* of partners after the group is formed, in which case nonrandom group formation is a confounding factor that needs to be accounted for. On the other hand, when focal individuals associate nonrandomly with partners, IGE can be defined to reflect not only the genetic basis of partner *influence* but also the role of partners' genotypes in *nonrandom group formation*. This definition may be appropriate, for example, when the goal is to predict phenotypic evolution. In that case, nonrandom group formation will not be considered a confounding factor but rather an integral part of IGE.

When nonrandom group formation is considered a confounding factor, the scope of confounding will depend on the underlying process. Phenotype-based partner choice, in the absence of other sources of confounding, will bias IGE studies only when the focal phenotype

is correlated with the trait(s) of focal individuals. By contrast, interactions with kin and population structure will affect IGE studies much more broadly because these processes induce a multitude of correlations between genetic and environmental factors experienced by focal individuals and their partners.

Detecting nonrandom group formation is not always straightforward. Whereas the presence of closely related individuals can often be determined either by tracking the individuals on a pedigree or from estimating relatedness from genomic data, population structure can be complex and subtle, and phenotype-based partner choice is poorly understood. Therefore, even when measures are taken to account for nonrandom group formation (see Part III), some confounding may remain.

Dealing With Unequal Interactions Within a Group

Even in carefully constructed social groups with random group composition, interactions within a group may vary in quantity and/or quality, resulting in different partners having different influences on the focal phenotype. Differences in number and intensity of interactions between social partners have been reported in IGE experiments on mosquitofish (Kraft et al., 2018) and fruit flies (Jaffe et al., 2020). When interactions inside the group vary in quantity and/or quality, IGE can be defined in 2 different ways. The simplest way is to ignore these differences and model equal IGE from all partners in the group. However, this approach may hinder our ability to detect IGE, for example if not all partners have the opportunity to exert their influence, as is the case in large cattle herds (Bijma, 2014). It may also result in confounding, whereby IGE will be interpreted as partner *influence* when they actually reflect a role of partner genotypes in having the *opportunity to influence* the focal individual. To avoid such confounding, when information on the quantity and/or quality of interactions in the group is available, one can condition upon these differences. It may be particularly useful to distinguish when profoundly different types of relationships are present within a group, such as when social hierarchies are present: pairs of submissive individuals may interact in completely different ways to pairs of dominant-submissive individuals.

Accounting for Confounding From Shared Environmental Effects, Relatedness, Population Structure, and Assortative Mating

In addition to sources of confounding factors that are specific to IGE studies (nonrandom group formation and unequal interactions within a group), similar sources of confounding that affect DGE studies can also affect IGE studies. Nonadditive effects generated when close relatives are (unknowingly) included in the study can bias estimates of additive DGE (narrow-sense heritability) and IGE alike. Shared environmental effects, which arise when multiple individuals experience a similar environment, are problematic when they affect genetically related individuals, which can happen when there is population structure (Vilhjálmsson and Nordborg, 2013), when close relatives are (unknowingly) included in the sample, or as a result of the experimental design (e.g., different inbred strains bred in different rooms). Assortative mating can also bias genetic estimates (Kemper et al., 2021). Finally, in GWAS population, structure and the inclusion of individuals with various degrees of relatedness can give rise to genetic background effects that can yield spurious associations if unaccounted for (Vilhjálmsson and Nordborg, 2013). In Box 2, we illustrate how these confounding factors, can bias IGE estimates or yield spurious IGE associations if ignored. For an illustration and the demonstration of the impact of assortative mating on studies of parental IGE, we refer the reader to Kong et al. (2018).

Nonadditive Effects across Partners

Most of the empirical data on IGE come from investigations in which effects of multiple partners are averaged or studies of pairwise interactions. Group dynamics and the resulting IGE are not always predictable from dyadic interactions, however. For example, Saltz (2013) found that dyadic interactions between pairs of genetically distinct *D. melanogaster* were influenced by the genotype of a third individual, and they denoted these effects as "second-order IGE." The inability to predict such nonadditive and nontransitive interactions might severely limit our ability to accurately estimate IGE or predict its evolutionary consequences.

Changes in IGE over Time

As outlined above, our ability to predict evolutionary change is compromised if IGE are ignored. However, prediction of evolutionary change over more than a single generation depends on assumptions about the constancy of genetic variance components (both direct and indirect) and of selection gradients, but all these parameters can themselves evolve (Steppan et al., 2002; Bailey and Desjonquères 2022, this issue; Chevin and Haller, 2014). Like other components of genetic variance, IGE variance depends on allele frequencies and effect sizes and is therefore likely to evolve under selection and vary across environments. Several empirical studies have reported that Ψ too can evolve (Chenoweth et al., 2010; Rebar et al., 2020), and that it can vary among populations, both over time in a single population and with changes in the abiotic environment (Bailey and Zuk, 2012; Signor et al., 2017a, 2017b).

IGE can also vary within the lifetime of an organism. Even if interacting groups remain constant, interactions between individuals within the group can vary over time. We can rarely track these changes, and their consequent effects on phenotypes, through each social experience an organism encounters during its life. Empirical studies have generally measured average effects of specific social environments over relatively long time scales (Peeters et al., 2012). However, averaging over long time periods can obscure effects that occur during critical periods of development.

Finally (and obviously), the membership of groups can change over time, which further complicates the identification and the phenotyping and/or genotyping of interacting partners. Relatively few animal studies monitor groups long enough to capture such changes (but see, e.g., McAdam et al., 2022). Studies of IGE in humans have a clear advantage here because self-reported social partners can shed light on changes in social groupings over the lifespan.

In this section, we have highlighted challenges that we view as especially pervasive and/or underappreciated in studies of IGE. In Part III, we describe solutions to some of these problems that can be provided by advances in study design, technologies for data collection, and statistical analysis.

III. Solutions and Prospects

Advances in study design as well as techniques for data collection and data analysis will facilitate and improve the analysis of IGE in the future. Below, we highlight some promising developments in each area.

Box 2. Examples of confounding and spurious effects in IGE studies

Here we illustrate several sources of confounding or statistical problems that can arise in IGE studies, using both hypothetical and documented examples, where available. We note that not all will apply to every study, as sources of confounding depend heavily on experimental design. We discuss potential solutions to these issues in Part III.

Correlation between focal environment and partner genotype. Consider a case in which parents are the partners and nestlings the focal individuals, with nestling weight as the focal phenotype (Figure 2.1). The body weight of nestlings sharing a nest could be more similar than average because they are fed by the same parents ***or*** because they are exposed to the same environmental conditions in the nest (wind, temperature, precipitation, etc.) and these conditions affect the focal phenotype. In this case, parental IGE cannot be distinguished from common environmental effects experienced by nestlings sharing a nest. Note that such confounding would occur even with a cross-fostering design in which all individuals are strictly unrelated because nestlings share both a parent and a nest. Also note that a shared partner is not the only way such confounding can arise: correlations between focal environment and partner genotype are also expected to arise when groups consist of closely related individuals (e.g., mouse littermates sharing a cage) or there is population structure (e.g., humans interacting with individuals living in the same area).

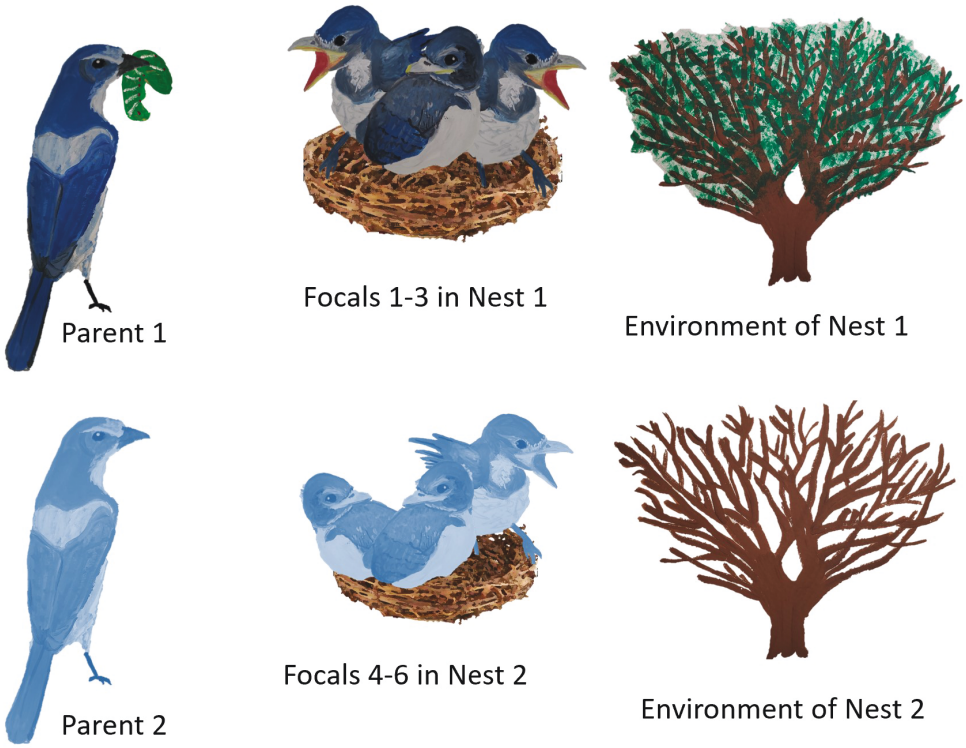

Figure 2.1. Example of correlation between focal environment and partner genotype.

Correlation between partner environment and partner genotype. The body weight of nestlings sharing a nest may be more similar than average because they are fed by the same parents ***or*** because their parents are exposed to environmental conditions (e.g., resource abundance) that affect parental care (Figure 2.2). In that case, parental IGE are confounded with environmental effects experienced by the parents. Importantly, such confounding can occur even when parental genotypes are not correlated with resource abundance. Consider an equivalent dataset in which each parent (genotype and environment) was replicated as many times as there are nestlings fed by the parent. This dataset would contain a correlation between parental genotypes and parental environments. Thus, even though parental genotypes and environments are, in fact, uncorrelated, confounding occurs. This example illustrates why both the genetic **and the nongenetic components** of indirect effects must be modeled to avoid confounding. We refer the reader to Bijma et al. (2007) for further discussion of this issue and the mathematical derivation of the nongenetic covariance between group members. In addition to experimental designs involving shared partners, correlations between partner environment and partner genotype can arise when closely related individuals are among the partners (whether these closely related individuals are in the same group or not) or there is population structure.

Correlation between direct and social genotypes. In agricultural settings, pigs that share a pen (enclosure) are often more genetically related than average because of organizational constraints/production techniques (Figure 2.3). As a result, their phenotypes can be more similar than average due to more similar DGE ***or*** due to more similar IGE from penmates (Bergsma et al., 2008). Similarly, in human genetics, greater concordance of monozygotic (MZ) twins compared to dizygotic (DZ) twins can be due, among other reasons, to more similar DGE in MZ twins compared to DZ twins ***or*** to more similar IGE from the other twin in MZ twins compared to DZ

Box 2. ***Continued***

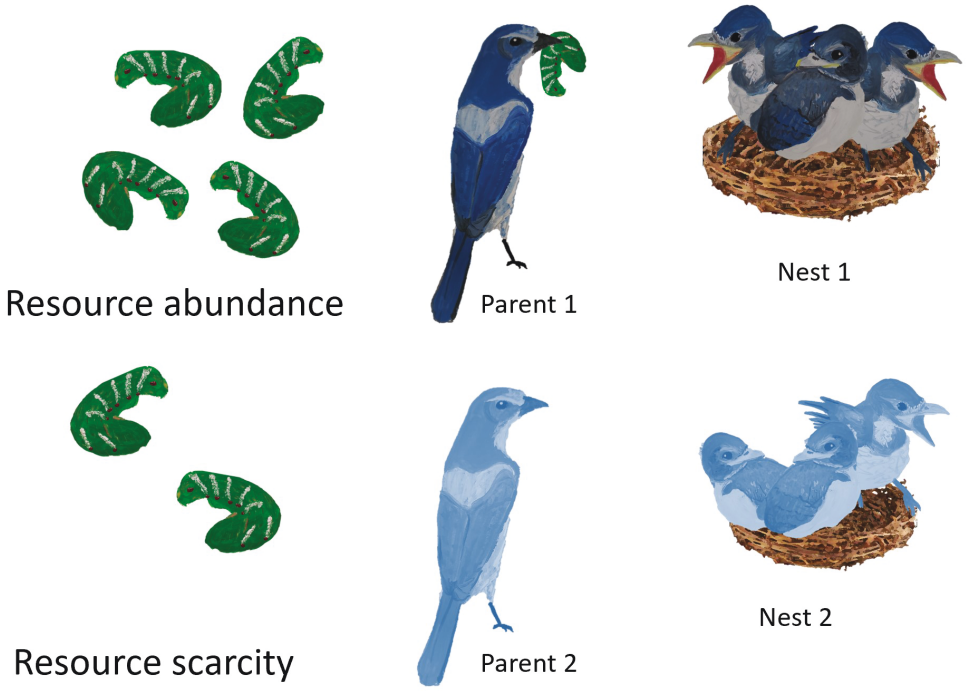

Figure 2.2. Example of correlation between partner environment and partner genotype.

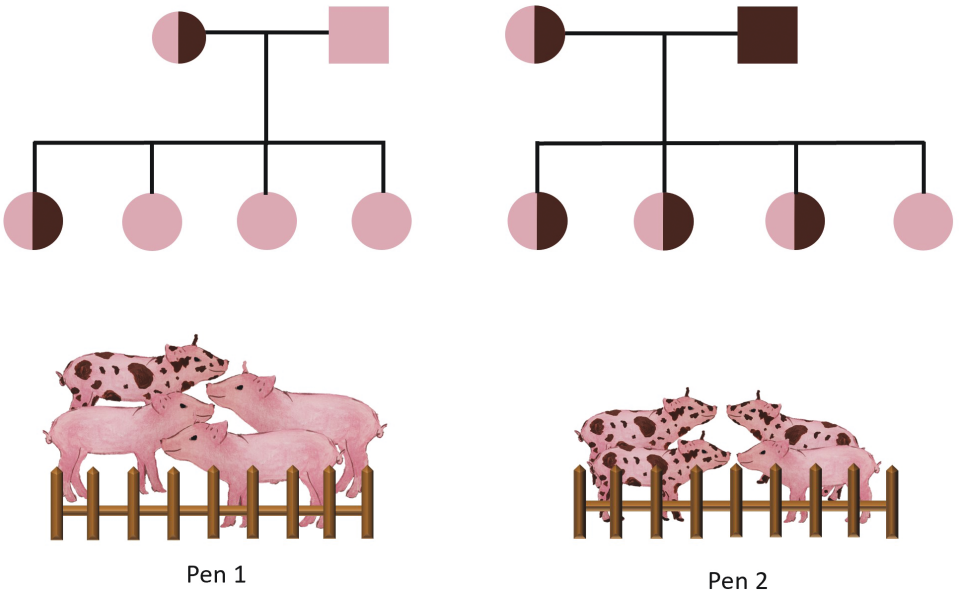

Figure 2.3. Example of correlation between direct and social genotypes.

twins. Finally, similar confounding could arise from population structure or from phenotype-based partner choice (see section on Nonrandom group formation).

Shared environmental effects in the presence of a positive correlation between DGE and IGE. Consider the growth of neighboring plants. Neighbors could be more similar than average because they are exposed to the same environmental conditions (shade) ***or*** because of a positive correlation between DGE and IGE whereby trait-increasing alleles of one plant help neighboring plants grow (e.g., ethylene-mediated cooperative effects discussed in Mutic and Wolf 2007) (Figure 2.4).

Background IGE in IGE mapping studies. In addition to spurious associations that can arise from confouding environmental effects, spurious associations in GWAS of IGE can arise from confounding by other, causal loci in the genome of partners (Figure 2.5),

Box 2. ***Continued***

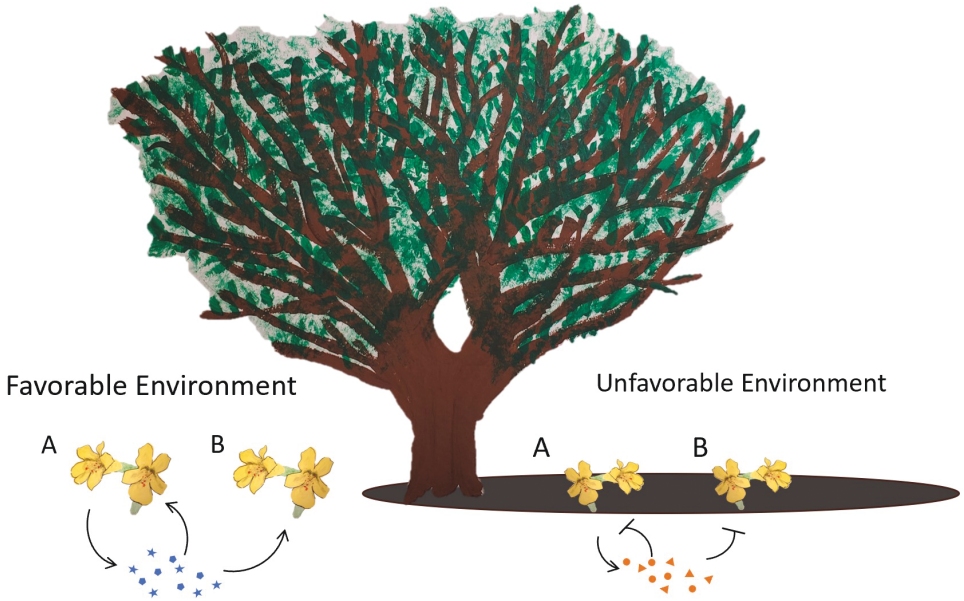

Figure 2.4. Example of shared environmental effects in the presence of a positive correlation between DGE and IGE.

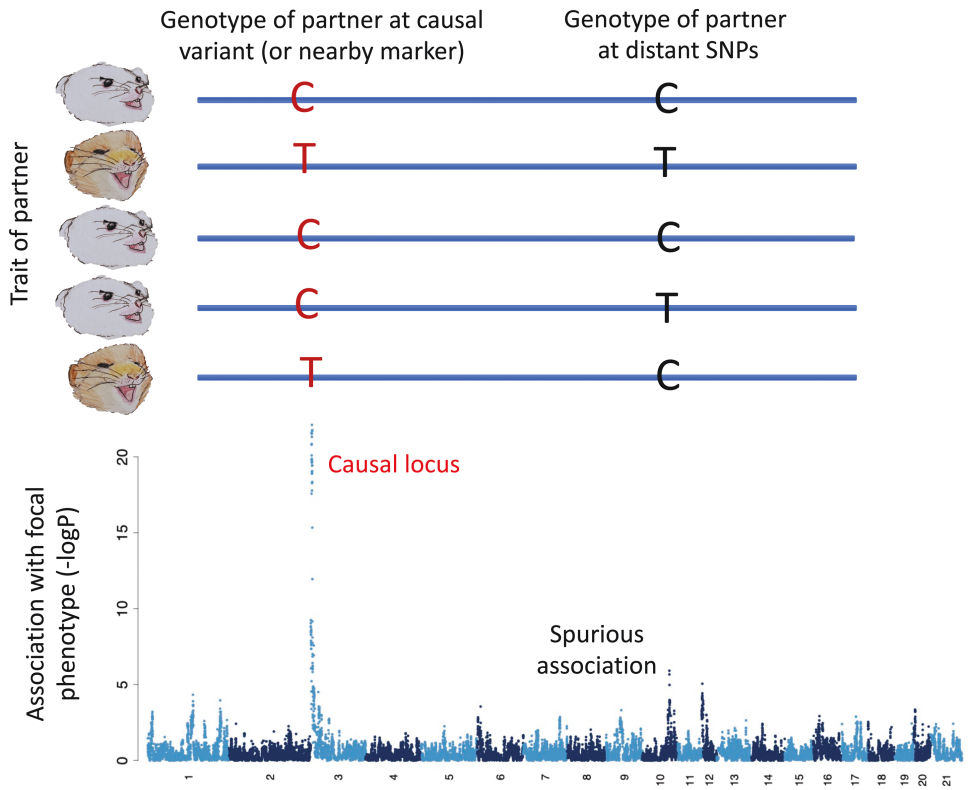

Figure 2.5. Theoretical illustration of a spurious association arising from the genoytpic correlation with a causal locus in an IGE mapping study.

similarly to how genetic background effects can give rise to spurious associations in GWAS of DGE (Vilhjálmsson and Nordborg, 2013). Background genetic effects are always present, but stronger in the presence of population structure or when the sample contains closely related individuals.

Larger sampling variance of the correlation between direct and social genotypes leading to anticonservative P-values in IGE mapping studies. In IGE mapping studies, when each individual in the study serves as both a focal individual *and* a partner, and DGE

Box 2. *Continued*

exist, *P*-values will not be calibrated under the null hypothesis of no IGE, resulting in anticonservative *P*-values unless local DGE are accounted for in the null model. This issue arises because the sampling variance of the correlation between direct and social genotypes in the case where each individual is both focal individual *and* partner is larger than naive expectation (i.e., random binomial draws, as would be the case if each individual was either focal individual *or* partner) (Figure 2.6, modified from Baud et al., 2021). Importantly, this is true even when all individuals are strictly unrelated.

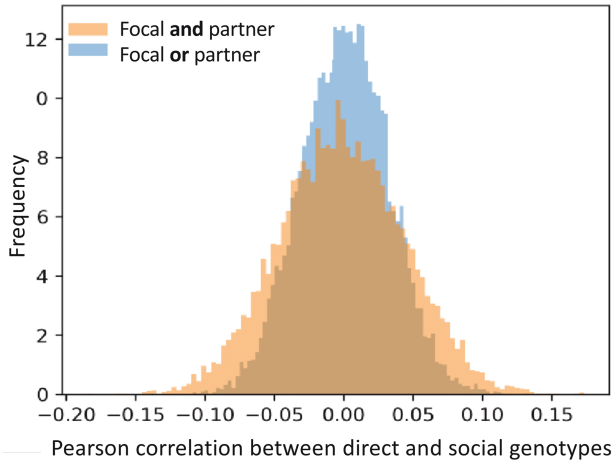

Figure 2.6. Greater sampling variance of the correlation between direct and social genotypes when each individual in the sample is used as both focal individual and social partner.

Study Design

1. Manipulating the Social Environment

Given the large scope for confounding described above, experiments aiming to manipulate the social environment have had and should continue to play a role in characterizing IGE. For example, when species exhibit discrete phenotypes that are suspected to generate IGE, manipulating the ratio of morphs in the social environment can demonstrate the existence of IGE and illuminate its importance in nature. This approach has been used to study IGE generated by the *GP-9* polymorphism in fire ants (Keller and Ross, 1998; Ross and Keller, 2002) and body-color polymorphism in eastern mosquitofish (Culumber et al., 2018; Kraft et al., 2018). When candidate genes for producing IGE are known, wild type and knock-out or knock-down strains can be compared with validate the candidates and quantify potential effects (Ferrero et al., 2013; Ribeiro et al., 2020). In the past, this kind of validation experiment has been limited to model systems with well-developed genetic resources. However, new genome-editing techniques should make this approach feasible in many non-model species (Huang et al., 2016; Mendoza and Trinh, 2018).

When the genetic variants and traits that produce IGE are unknown, the social genetic environment cannot be purposefully manipulated in the same way, but variation in social partners can still be experimentally controlled. For example, IGE can be identified by contrasting the social effects of different inbred strains when these are available (Bleakley and Brodie, 2009; Ferrero et al., 2013; Liu et al., 2017; Jaffe et al., 2020). If interest lies in IGE that potentially occur in nature, as in evolutionary biology, we note that this kind of controlled experiment can mainly reveal the *potential* for such effects. However, many species do not naturally inbreed, and inbred strains even if derived from natural populations, can be unrepresentative of natural genotypes and their interactions because of inbreeding depression. In laboratory studies, this problem can be alleviated by making use of F1 crosses between inbred strains derived from nature (e.g., Saltz et al., 2012) or using later generations of intercrosses between wild-derived strains (Walsh et al., 2022). These populations more closely reflect the allele and genotype frequencies and the associated phenotypic variation, found in their natural source populations. Of course, environmental conditions can also differ dramatically between laboratory and natural populations. Field manipulations of individuals that naturally form discrete groups provide promising material for illuminating IGE in nature; manipulations of social groups in nature have been conducted of forked fungus beetles, for example, which form discrete groups on bracket fungi (Brodie, 2022) and in guppies, which inhabit discrete pools in rivers (Hughes et al., 2013). To date, however these manipulations have been based on phenotypic, but not genetic differences among individuals.

For organisms in which social groups are difficult or impossible to manipulate, video or audio playback, dummies, or robots can be used to manipulate social interactions in species that respond in naturalistic ways to these stimuli. This kind of manipulation has been used extensively in behavioral ecology (Naik et al., 2020, and references therein), but has been rare in the IGE literature (but see Bailey and Zuk, 2012 for an example). The increasing sophistication of technologies like robotics and artificial intelligence should make this approach increasingly feasible in many systems (Landgraf et al., 2021).

2. Randomizing the Social Environment

When the genotypes of partners cannot be partitioned into meaningful groups—typically when an outbred or recombinant inbred population is studied and the focus is on IGE aggregated across the genome rather than IGE at a single locus—the social environment can still be *randomized* with respect to specific confounding

factors. For example, when studying IGE from cagemates in outbred laboratory rodents, it is possible to use a single offspring per parental pair or to spread the offspring of a pair across cages to avoid confounding of IGE by parental/litter effects. Furthermore, as the animals do not choose their cages but rather are assigned to specific cages by the experimenter, partner choice cannot be involved in any detected association between focal phenotype and partner genotype. To study parental IGE, and more precisely the *influence* of parents on offspring and vice versa, cross-fostering experiments are possible in some species and the "natural experiment" created by adoption has been used in humans. Cross-fostering removes the passive correlation existing between parental and offspring genotypes, such that associations between parents and offspring can be interpreted as *influence*. Cross-fostering has been used in laboratory mice to gain insights into maternal, offspring and sibling IGE in early life (Ashbrook et al., 2015, 2017). Cross-fostering has been used a great deal in studies of free-living birds (e.g., Verhulst and Nilsson, 2008), but not, to our knowledge, to investigate IGE. In humans, adoption studies have provided evidence of parental genetic effects on educational attainment (Cheesman et al., 2020).

3. Longitudinal Studies With Repeated Measures

Whereas manipulating and randomizing the social environment helps *avoid* confounding, longitudinal studies with repeated measures provide the ability to account for many confounding factors. In the example illustrated in Figure 2.1 (Box 2), confounding between rearing environmental effects (nest) and parental IGE could be accounted for if multiple broods/litters reared in different environments were included for each parent, and rearing environment was modeled explicitly. Repeated measures will be particularly valuable to disentangle nonrandom group formation from partner influence, as one can model the evolution of focal and partner phenotypes over time to look specifically for partner influence (Martin and Jaeggi, 2021).

Data Collection

IGE studies always require the ability to measure interactions between individuals (e.g., defining social groups or measuring the distance between plants), the focal phenotypes, and either the genotypes or relatedness of social partners or the trait(s) of partners thought to be mediating the IGE. Note that, in some cases, the focal phenotype and the trait of partners mediating IGE are the same, but here we consider the general case where the focal phenotype and the trait of partners mediating IGE are different.

1. Automatic Scoring of Interactions

Recent advances in technologies for tracking animal movements as well as machine learning approaches and social network theory are poised to allow behavioral ecologists and animal breeders to study interactions at unprecedented scales, facilitating the identification of interacting partners over time and automating the scoring of behavioral interactions (Smith and Pinter-Wollman, 2021). These technological advances may make it feasible to increase sample sizes and therefore the power to detect IGE, and to characterize variation in behavioral interactions within a group.

Social encounters can be detected directly using proximity loggers that record instances when 2 tagged individuals come within a certain distance. Alternatively, they can be inferred indirectly from data on the movements and spatiotemporal locations of animals (e.g., data from VHF radio telemetry tags, GPS loggers, RFID tags, and Bluetooth and GPS technology; reviewed in Krause et al., 2013; see also Stopczynski et al., 2013 and Sandeepa et al., 2020). Another common approach for both detecting social interactions and quantifying how individuals interact is to analyze video recordings. Machine learning approaches now enable automated analysis of social interactions from video recordings of both barcoded individuals (e.g., Gernat et al., 2018) and unmarked individuals (Guzhva et al., 2016; Arac et al., 2019; Foris et al., 2019; Romero-Ferrero et al., 2019). A powerful approach for tracking individual behavior and quantifying social interactions is to combine video analysis and RFID technology (e.g., Weissbrod et al., 2013; Ellen et al., 2019) or lightweight backpack-mounted barcodes (e.g., Alarcón-Nieto et al., 2018). Finally, our ability to study social interactions has greatly advanced with the development of social network analysis methods (Wey et al., 2008; Farine and Whitehead, 2015; Finn et al., 2019).

2. High-Throughput Phenotyping (Many Animals and Many Phenotypes for Each Animal)

Technological advances that permit high-throughput phenotyping will help overcome several limitations of current IGE studies, and new data analytic techniques can alleviate the multiple testing problem associated with analyzing many different phenotypes (see the Data analysis section). First, large sample sizes are required to estimate the correlation between DGE and IGE, which can shed light on the collaborative or competitive nature of IGE and the role of "spread" in IGE (Baud et al., 2021). Large samples are also required to leverage the equivalence between trait-based and variance-component models (McGlothlin and Brodie, 2009), and to identify individual genetic loci underlying IGE, especially when DGE and IGE are confounded (Baud et al., 2021). Second, characterizing the phenome of focal individuals permits detecting IGE on phenotypes that were not previously known or suspected to be affected by IGE (Baud et al., 2017; Xia et al., 2021), while characterizing the phenome of interacting partners will point to the types of traits of partners mediating IGE (e.g., behavioral, immune-related, or metabolic traits), thereby helping to uncover unexpected mechanisms underlying IGE.

Phenotyping large samples can be achieved using various modalities and technologies (Tardieu et al., 2017; Brito et al., 2020; Canario et al., 2020). One of the most widely used strategies is video-recording followed by computer-aided image analysis, which have been used to infer gait and grooming behavior in mouse (Geuther et al., 2021; Sheppard et al., 2021), aging and lifespan in *C. elegans* (Stroustrup et al., 2013), and body conformation in cattle (Nye et al., 2020; Long et al., 2020). Imaging technologies have also been used for high-throughput phenotyping in plants (Fahlgren et al., 2015; Rahaman et al., 2015). Other widely used automatic, high-throughput, phenotyping strategies involve wearing specialized gear coupled with specialized detection apparatuses (e.g., RFID tags are used by automated milking robots to measure milk production by individual cows, wrist bands and watches are used to track heart rate and sleep and humans). In humans, additional strategies are available in the form of electronic health records, which in some cases are connected to individual genomic data, and questionnaires connected to individual genomic data (e.g., 23andMe). In addition to characterizing entire organisms, biological samples can provide rich phenotypic data for phenomics. For example, biochemical, hematological, and immunological analyses can provide a broad representation of

the physiology of an organism, and -omics analyses can shed light on the function of a particular tissue.

3. Dense Genotyping Using Next-Generation Sequencing

The ability to obtain dense genotyping data for all focal individuals and their partners can greatly advance our understanding of IGEs. Genomic data can help identify relationships among individuals, characterize population structure, and shed light on potential mechanisms underlying IGE via GWAS approaches. Next-generation sequencing technologies (Metzker, 2010; Levy and Myers, 2016) provide many options for high-throughput single-nucleotide polymorphism discovery and genotyping, both with or without an existing reference genome (though de novo genome assembly is now possible in most organisms; see Rice and Green, 2019 for a review of current advancements in genome assembly methods). Genotyping methods using next-generation sequencing and their applications have been nicely summarized elsewhere (Ekblom and Galindo, 2011; Nielsen et al., 2011; da Fonseca et al., 2016). Furthermore, genotype imputation is an efficient method for generating high density genotypes for many individuals from a mix of high density genotype data for a subset of individuals and low-density genotype data (e.g., from shallow whole genome resequencing) for the rest of the sample (Li et al., 2009), or from low-density genotype for all individuals, provided that a high-quality reference panel exists. All genotype imputation approaches rely on identifying shared haplotypes between individuals: between related individuals on a pedigree, between a sample of unrelated individuals and individuals in a large reference panel, or between unrelated individuals. Different genotype imputation methods are reviewed in Li et al. (2009); Marchini and Howie (2010); Das et al. (2018); Ullah et al. (2019).

Data Analysis

1. Improved Statistical Models to Account for Confounding

Confounding cannot always be avoided experimentally, in which case confounding factors need to be accounted for in the statistical models used for parameter estimation and statistical inference. Much of the confounding described in Part II and Box 2 can be accounted for using the appropriate random effects. In particular, jointly modeling DGE and IGE in variance-component models prevents bias due to DGE and any environmental effect covarying with DGE, which is particularly important when groups consist of related individuals or there is population structure. In the absence of a random DGE term in the model, IGE estimates would be biased. In statistical inference (when testing whether the IGE variance component is different from 0), confounding is detrimental whether it is accounted for or not: confounding results in anticonservative *P*-values if unaccounted for, and conservative *P*-values if accounted for (by including a random DGE term in the null model).

Modeling the nongenetic component of indirect effects is also key to avoiding biased estimates of IGE. Indeed, nongenetic indirect effects contribute to phenotypic covariance when focal individuals share one or more partner(s) (see Figure 2.2 in Box 2) and when direct and indirect nongenetic effects are correlated (e.g., if a mouse were dropped on the ground while being transferred to a different cage, the stress levels of the mouse would increase and the mouse could communicate its stress to its cage mates). Part or all of this nongenetic covariance may be captured by IGE if nongenetic indirect effects are not modeled explicitly, resulting in biased estimates of IGE. We refer the reader to (Bijma et al., 2007) for further discussion of this issue and the mathematical derivation of the nongenetic covariance between group members.

Additional random effects can be included to account for common environmental effects shared by all group mates (e.g., pen effects as in Bijma et al., 2007) or by subsets of partners (e.g., littermates). When repeated measures have been collected in longitudinal studies, sophisticated statistical models exist that provide an even better handle on confounding factors and permit the characterization of feedback between interacting individuals, effectively distinguishing between nonrandom group formation and influence (Martin and Jaeggi, 2021).

Finally, in IGE mapping studies, in addition to including appropriate random effects as detailed above, an IGE random term should be used in the null and alternative models to avoid spurious associations arising when the social partners of the focal individuals include related individuals (whether they are in the same group or not) or when there is population structure. Background IGE and environmental effects correlated with partner genotypes could yield spurious IGE associations (following the same reasoning as discussed by Vilhjálmsson and Nordborg, 2013 for DGE studies). Note that this correction will not be perfect if background effects are oligogenic rather than polygenic or if shared environmental effects do not vary linearly with the degree of genetic similarity between interacting partners. Furthermore, a fixed effect needs to be included in the null and alternative models to account for local DGE when the genotypes of focal individuals and partners are correlated due to relatedness or population structure and in study designs in which each individual serves as both a focal individual and social partner (Figure 2.6 in Box 2).

2. Statistical Models to Leverage High-Throughput Data

When multiple phenotypes have been collected on focal individuals to study a biological function of interest, they can be analyzed independently using univariate models, analyzed jointly using multivariate analyses, or analyzed using dimensionality reduction techniques. Univariate analyses, which are the most widely used, can estimate IGE parameters with moderate sample sizes but pay a high penalty in statistical inference (hypothesis testing) when many phenotypes are studied because of the need to account for multiple testing. Multivariate analyses can be carried out with moderate sample sizes and reduce the multiple testing burden, but only if strong assumptions are made regarding the model parameters, typically by assuming genetic effects are uniform across phenotypes. Relaxing these assumptions implies estimating and/or testing a larger number of parameters, which requires much larger sample sizes and leads to a multiple testing issue. Bivariate variance-component IGE models have been developed (Peeters et al., 2012) that can be used to probe pairs of focal phenotypes. Finally, dimensionality reduction techniques, such as structural equation modeling or generalized network modeling, provide a tractable way to deal with high dimensional phenotype data (Araya-Ajoy and Dingemanse, 2014; Martin and Jaeggi, 2021).

3. Molecular Genetics Approaches to Dissect the Mechanisms of IGE

Molecular genetics is increasingly contributing to dissecting the mechanisms of IGE, more specifically identifying the traits of partners mediating IGE. First, methods such as the GWAS, can identify individual genomic loci giving rise to IGE, which in some cases permits identifying putatively causal IGE genes and traits of social

partners influencing the phenotype of interest (e.g., Mutic and Wolf, 2007; Bailey and Hoskins, 2014; Baud et al., 2021). For example, in a GWAS of IGE arising between laboratory mice sharing a cage, Baud et al. (2021) identified *Epha4* as a gene giving rise to IGE on stress-coping strategy and wound healing. This finding, together with reported patterns of expression and documented functions of *Epha4* in the body, led to the formulation of specific hypotheses about the traits of cage mates mediating IGE. It also permitted the development of a simplified experimental paradigm comparing focal individuals co-housed with either *Epha4* knock-out or wild-type littermates, which will help further dissect the mechanisms of IGE experimentally.

Second, when estimates of DGE effect sizes already exist for a given trait (i.e., a well-powered GWAS of DGE for that trait has already been performed) and partners in the study sample have been genotyped, one can use polygenic scores that predict trait values of partners to study IGE (e.g., Kong et al., 2018; Sotoudeh et al., 2019). This approach is very valuable as it permits leveraging GWAS of DGE to maximize power in IGE studies. However, one should bear in mind that that GWAS effect sizes can be biased by uncorrected population structure and assortative mating (Mathieson and McVean, 2012; Berg et al., 2019; Sohail et al., 2019) as well as by familial IGE experienced by GWAS participants (Trejo and Domingue, 2018). Hence, results need to be interpreted with care.

Finally, Mendelian randomization is an approach first developed in genetic epidemiology that uses genetic variants to assess causal relationships among traits (Davey Smith and Ebrahim, 2003) and that has been used to evaluate the causal effect of partner traits on focal phenotype in humans (e.g., Warrington et al., 2019). Mendelian randomization makes numerous assumptions, however, which need to be evaluated rigorously before reaching conclusions (e.g., population structure and assortative mating; Hartwig et al., 2018; Brumpton et al., 2020).

IV. Conclusions

Empirical investigation of IGE, and their relationship to DGE, are poised to answer fundamental questions in ecology and evolutionary biology, agricultural biology, and biomedical genetics. To realize this potential, however, substantial challenges need to be addressed. Large sample sizes are necessary to estimate and map IGE, which may be difficult to achieve in studies of free-living (nonhuman) organisms and which increases the risk of confounding from uncontrolled experimental factors. Automatic tracking and phenotyping, together with high-throughput genotyping, can help to increase sample size and collect repeated measures in these studies. Nevertheless, it is worth thinking carefully about the kinds of organisms where one can acquire genetic and phenomic data, along with detailed information on social interactions, in thousands of individuals. Plants and other non-motile organisms have been underutilized in the study of IGE, but species with prolonged non-motile life stages and short life cycles could be especially suitable for these investigations. Developmental and longitudinal studies could also be easier in such species. Expanding the range of taxa used could address a major gap: compared with biomedical genetics, other fields have not generated as many data sets useful for mapping genetic variants that cause IGE. Although differences in research budgets and in the availability of community-wide genetic resources are a major contributor to this gap, another factor might be an underappreciation of the insight provided by these approaches.

High-throughput phenotyping is likely to be challenging in all disciplines. Community-based resources, such as genetic reference panels, have been usefully deployed by mouse, fly, and *Arabadopsis* quantitative geneticists, and similar panels could be produced for other species. Prime species for the development of reference panels will be those that reproduce asexually (many plants, animals, and microbes) or naturally inbreed. However, outbred populations can also be used as reference populations since alleles are still replicated across outbred individuals. Community resources also reduce the costs and logistical challenges associated with genotyping or sequencing large numbers of individuals or strains.

Finally, a general recommendation is to engage in more crosstalk across disciplines. For example, sources of confounding have been more extensively discussed in the human genetics literature, but these concerns are equally relevant in agricultural and evolutionary studies (see, e.g., Bailey and Desjonquères, 2022). In contrast, human geneticists could take inspiration from the use of automated tracking and phenotyping in agricultural and evolutionary biology, although, of course, informed consent and other ethical considerations need to be addressed. We hope the integration of principles and approaches described in this perspective can facilitate such crosstalk.

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