



## SYMPOSIUM

# “Homeostatic Hitchhiking”: A Mechanism for the Evolutionary Retention of Complex Adaptations

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From the symposium “Hormone-Mediated Sex Ratio Adjustment in Vertebrates” presented at the annual meeting of the Society for Integrative and Comparative Biology, January 3–7, 2013 at San Francisco, California.

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**Synopsis** The complexity of organismal organization channels and accommodates novel genomic and developmental modifications. Here, I extend this perspective to suggest that emergent processes that dominate homeostasis—co-option, re-use, and recombination of accumulated elements—can create configurations and dependencies among these elements that strongly reduce the number of evolutionary steps needed for the evolution of precise novel adaptations. Evolutionary retention and environmental matching of such configurations are further facilitated when they include elements of homeostasis that are responsive to particular environmental cues. I apply this perspective to the study of evolution of sex-biased egg-laying in birds, a phenomenon that combines precision, complexity, context-dependency, and reversibility. I show that homeostatic hitchhiking can overcome the main difficulty in the evolution of this adaptation—the perceived necessity of *de novo* co-evolution of oogenesis, sex-determination, and order of ovulation in each environmental context—something that would require unrealistic expectations of evolutionary rates and population sizes and is not a desirable outcome for a process that needs to retain substantial environmental sensitivity. First, I explain the rationale behind the homeostatic-hitchhiking hypothesis and outline its predictions specifically for studies of sex-bias in order of egg-laying. Second, I show that a combination of self-regulatory and emergent processes and ubiquitous re-use of conserved growth factors make oogenesis particularly amenable to homeostatic hitchhiking. Third, I review empirical evidence for this mechanism in the rapid evolution of adaptive sex-biased order of egg-laying that accompanied colonization of North America by the house finch (*Carpodacus mexicanus*).

## Introduction

Evolution of complex adaptations—that combine precise environmental contingency with stability of pre-evolved components—is a contentious issue (Reid 1985; Oyama 2000; West-Eberhard 2003; Hall et al. 2004; Sansom and Brandon 2007). The challenge comes from two directions. First, from a structural point of view, it is difficult to envision genomic or phenotypic architecture that enables accommodation of novel environmental or genetic input, and at the same time, stability of already evolved adaptive structures (Maynard Smith 1970; Gavrillets 2004; Wagner 2011)—that is, evolution of adaptations that are sensitive to “external” cues in their expression and yet “internally” precise in their composition (West-Eberhard 2003). Second, the strength of natural selection is proportional to the effective

population size and thus, from a population genetics perspective, the evolution of complex, precise, and reversible adaptations requires efficacy of selection (Lynch and Abegg 2010) that is rarely achieved in animal populations in which these patterns are routinely observed. The relative rarity of environmental contexts that favor an expression of a particular adaptation, associated requirement for conditional expression and reversibility of mechanisms that produce adaptation further weakens the efficacy of such selection. Yet, the literature of behavioral and physiological ecology is replete with empirical examples of composite structures that are only adaptive when they have an immediate and exact match to a particular environmental context (e.g., quality of mates or availability of food).

Traditional resolution of this paradox has been to suggest that the mechanisms behind the origin of such adaptations are distinct from the mechanisms that maintain them and accomplish their expression in a particular environmental context. Most conventional treatments, however, assume that both of these groups of mechanisms are different versions of natural selection. For example, a direct extension of the Darwinian view suggests that development is best understood as a collection of past adaptations (reviewed by Badyaev 2011b), with a caveat that the contemporary expression of novel adaptations is biased, and sometimes channeled, by accumulated elements of past adaptations (Baldwin 1896; Schmalhausen 1938; Maynard Smith et al. 1985; Wagner et al. 1997; Ancel 1999). Successive accumulation of organism–environment configurations over many generations is assumed to be accommodated by organismal homeostasis, and the most recurrent of such configurations become stabilized by genetic networks (Oyama 1988; Newman and Müller 2000). When present and past environmental contexts match, past adaptations get expressed (Chetverikov 1926; Gause 1940; Wagner 2003; Young and Badyaev 2007). Thus, the historical experience of an organismal lineage shapes the pathways available for its evolution: “the history of current adaptation cannot be uncoupled from the history of the organism” (Schmalhausen 1938; see also Dobzhansky 1974).

Another perspective comes from recent studies of the prevalence of nonadaptive processes in evolution, and the realization that a significant portion of organismal, and particularly genomic, organization has evolved by processes that have more to do with maintaining cohesiveness of structures than with specific adaptations that improve their performance in a particular environment (Lynch 2007b; Koonin 2011). This perspective suggests that accumulation of organismal complexity in relatively small populations is an inevitable consequence of weak purifying selection; the ability to persist despite accumulation of deleterious elements is a hallmark of evolution of populations that experience weak selection. Such complexity and inability to eliminate deleterious elements in small populations elevates homeostatic processes to the role of main player in such populations—the mechanism that both accommodates novel inputs and directs responses to environmental variation.

That accumulated organismal complexity (neutral or adaptive in origin) channels and accommodates novel genomic and developmental modifications, and that some of these modifications can be adaptive (the Baldwin effect), has been suggested repeatedly

throughout the history of evolutionary biology (Osborn 1896; Baldwin 1902; Schmalhausen 1949; Whyte 1965). The perspective outlined here extends these views to suggest that emergent processes that dominate homeostasis—co-option, recombination, and re-wiring of accumulated elements—can occasionally create configurations that greatly reduce the number of steps needed for evolution of precise novel adaptations (West-Eberhard 1989; Stern 1999; Stoltzfus 1999; Gerhart and Kirschner 2007; Reid 2007). This is because the recombined and newly recruited elements include components of past adaptations (and thus their past environmental contingencies). Evolutionary retention and matching of such configurations to beneficial environments are accomplished when such configurations include elements of physiological homeostasis that are responsive to particular environments. Most recurrent associations between these emergent processes and elements of homeostasis could, in principle, accumulate greater genetic redundancy and stabilization that will assure their reliable expression in particular environmental conditions (Salazar-Ciudad et al. 2001; West-Eberhard 2003; Newman 2005; Reid 2007). However, it is neither a necessary, nor a likely outcome (given the inefficacy of natural selection in accomplishing such fixation). Instead, a combination of such arising developmental and physiological configurations and dependencies among elements of past adaptations (i.e., cooption of developmental modules), and elements of homeostasis that underlie organismal response to the current environment, can produce exactly the kind of adaptation that combines environmental matching and sensitivity with precision of expressed configurations.

This process might be thought of as “homeostatic hitchhiking,” by analogy with genetic hitchhiking—the process whereby a selectively neutral allele can nevertheless propagate in a population and evolve by association with positively selected elements of genetic architecture. In the case of homeostatic hitchhiking, elements of adaptation evolve by harnessing elements of physiological homeostasis that themselves do not have much to do with this specific adaptation. The process capitalizes specifically on two components of physiological homeostasis—its environmental sensitivity and its maintenance of organismal functioning under variable environmental conditions. Here, I will review and test general predictions of this mechanism for the evolution of sex-biased order of egg-laying in birds—a widespread adaptation that combines seemingly evolutionary impossible coordination of precision, complexity, context-dependency, and reversibility.

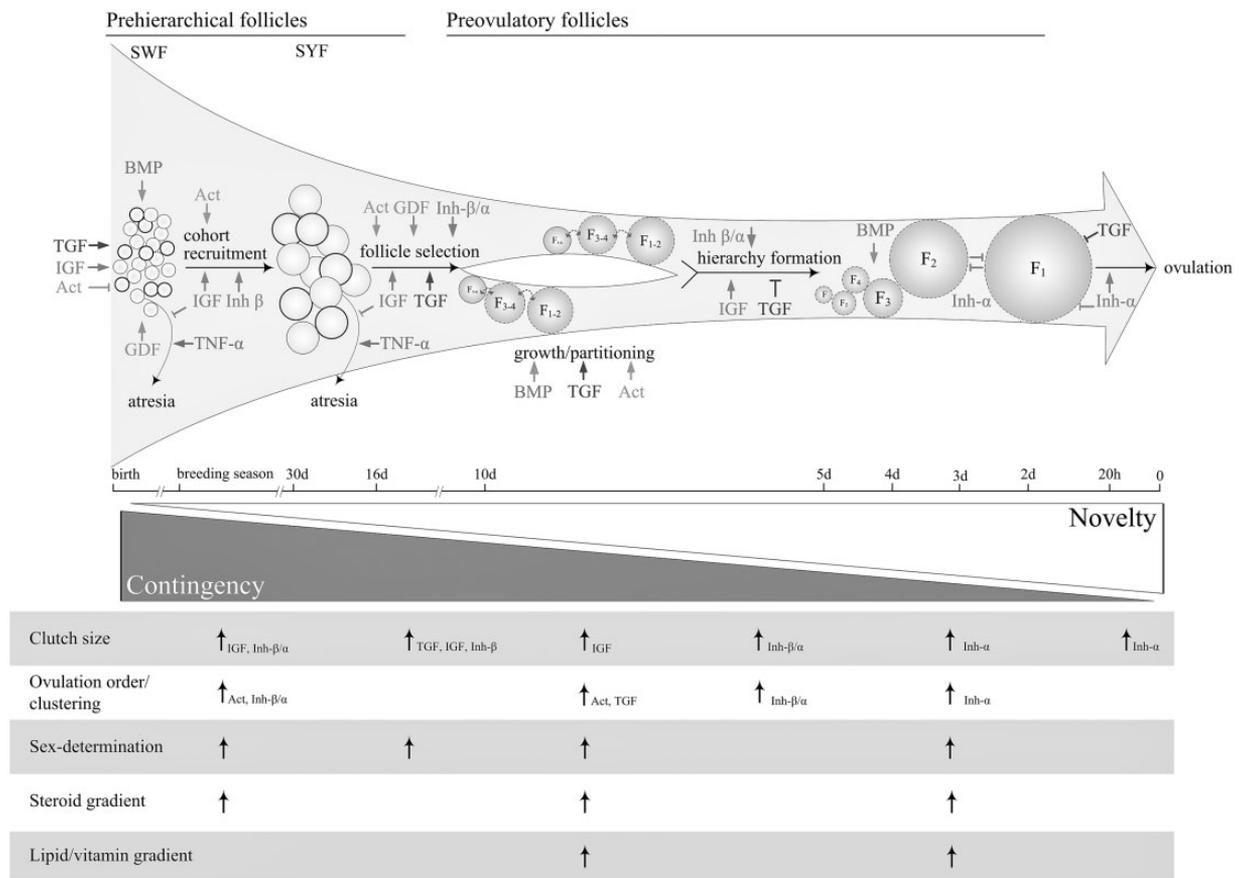
## Evolution of sex-biased order of egg-laying: Reconciling precision and context-dependency

Birds lay eggs gradually, over multiple days, and this often produces asynchrony in hatching—a phenomenon in which nestlings from eggs laid early and those laid later have distinct developmental times and modes of growth (Clark and Wilson 1981; Ricklefs 1993). The evolutionary and ecological significance of asynchrony of hatching is particularly strong when it is combined with sex-specific patterns of growth and with sequential bias in production of male- and female-bearing eggs in a clutch (Krackow 1995; Magrath et al. 2003). In such contexts, sex-biased order of egg-laying and associated hatching asynchrony is frequently co-opted for a variety of adaptations. In some species, it is a powerful way to increase variation among offspring, which is particularly important in species that colonize new environments (Badyaev 2005); in other species, hatching order becomes associated with expression of behavior—for example, aggression or dispersal (Duckworth 2009). In some populations, females produce complex sequences of male- and female-bearing eggs that are highly repeatable across similar contexts; in others, sex-bias forms a gradient in egg-laying sequence (Ankney 1982; Cordero et al. 2001; Velando et al. 2002). These adjustments often have strong consequences for fitness, in a number of species even enabling persistence of populations. However, just because traits or structures are currently maintained by natural selection, does not mean that they have evolved by natural selection (Gould and Lewontin 1979; Müller and Newman 2003). Here, I will examine evidence for a nonadaptive origin of complex and reversible coordination of oogenesis, sex-determination, and ovulation-order—components that form the basis for sex-biased ovulation-order in birds. I will suggest that natural selection that results from matching these components to the environment can be particularly effective when such combinations are not random.

At first, noninvolvement of natural selection might seem like a paradoxical suggestion—one typically thinks of complex, coordinated, and precise features (especially those that are current adaptations)—as the product of natural selection. However, there are several issues—some conceptual and some technical—that need to be considered before natural selection is implicated in the *origin* of sex-biased order of egg-laying. The most important of these is the basic population genetics postulate that effectiveness of natural selection is proportional to an

effective population size that defines minimum waiting times and population sizes required even for most beneficial and simple modification to be fixed by natural selection (e.g., Lynch and Abegg 2010). Complexity and contingency of these adaptations, very small population sizes, immediacy of the observed response to specific environmental cues, and relative rarity of contexts in which such adjustments are beneficial (Legge et al. 2001; Andersson et al. 2003; Arnold and Griffiths 2003; Müller et al. 2003), all make natural selection an unlikely mechanism whereby such features originate. That is, unless some physiological, developmental, or genetic “shortcuts” mitigate the issues of complexity of adaptations and small population sizes. Furthermore, in some environmental contexts, a precise adjustment of sex-bias in order of egg-laying is beneficial only when fully expressed (e.g., males produced in the second-laid egg and females in the fifth-laid egg), such that incomplete or intermediate steps do not confer partial fitness benefits (e.g., Dzus et al. 1996; Badyaev et al. 2002). Thus, although precise modifications of sex-biased order of egg-laying are commonly adaptive—that is, are subject to current natural selection—we need to consider other hypotheses for the *origin* of these features. One such alternative—“homeostatic hitchhiking”—makes three general predictions.

First, the developmental dynamics of self-regulatory and modular core processes of oogenesis can produce nonrandom combinations of oocyte growth, sex-determination, and order of ovulation (reviewed by Badyaev 2011a). Such non-random combinations amount to an important “shortcut” for natural selection; when the role of natural selection is limited to eliminating non-survivable combinations of these processes as opposed to creating these combinations, selection can be more effective. Second, weak natural selection means not only that it is difficult to create novel structures but also that it is difficult to eliminate accumulated structures, even those that are detrimental to the organism’s survival. Such that retention and conservation of genomic or phenotypic elements over evolutionary time does not necessarily imply fixation by natural selection, but could instead reflect weak purifying selection (Lynch 2007a). Such accumulation of elements (some of which are, inevitably, components of past adaptations) under weak selection can lead to the emergence of novel combinations and dependencies among them, for example, “junk-to-function” transitions (Stoltzfus 1999; Reid 2007; Koonin 2011). In relation to coordination of oogenesis, sex-determination, and order of ovulation, this hypothesis predicts



**Fig. 1** Conserved growth factors produce context- and stage-specific modulation of the effects of organism-wide signaling of FSH and LH. Growth factors are TGF: transforming growth factor-β; IGF: insulin-like growth factor; TNF-α: tumor necrosis factor-α; BMP: bone morphogenetic proteins; Inh-β and Inh-α: inhibin-α, -β, and β/α ratio; and Act: activin. At the onset of breeding season, cohorts of small white follicles are advanced to the small yellow follicle stage; the order of recruitment is linked with initial acquisition of ability to transport yolk across membranes. Preovulatory follicles partition (double-headed arrows) liver-produced yolk precursors with adjacent follicles in their groups and eventually merge into a common ovulatory hierarchy guided by disproportional growth and associated spatial effects of inhibin-signaling by the largest follicle (F<sub>1</sub>). The LH surge that causes F<sub>1</sub> to ovulate simultaneously stops growth of F<sub>2</sub> and advances it to the stage of ovulation. Elements of oogenesis and their potential homeostatic associations differ in environmental contingency—from completely unique and novel events on the right side of the time-arrow to highly recurrent events on the left (see text for details). Table shows stages and growth factors (when known) that regulate adaptive changes in clutch size, ovulation-order, sex-determination, and gradients of hormones and morphogens in a clutch. Modified from Badyaev (2011a).

ubiquitous re-use and persistence of the same regulatory elements throughout oogenesis and at different levels of organization (Fig. 1). The third prediction is based on the realization that despite weak selection for the maintenance of specific context-dependent functions, natural selection is effective in maintaining the cohesiveness and homeostasis of an organism. This is because such homeostatic selection (e.g., internal selection) is uniform across external contexts (Schmalhausen 1938; Whyte 1965; Newman 2006; Reid 2007). Thus, harnessing an element of homeostasis could be an effective way of matching complex orders of egg-laying (produced by modular developmental processes) with the most beneficial environmental context.

## Evidence

### Ubiquitous co-option and re-use of regulatory elements

During the breeding season, the avian ovary contains three groups of follicles: small white follicles that are produced by germ cells in an embryo, small yellow follicles that are recruited at different times and in several small batches from the first group at each breeding season, and preovulatory follicles that are recruited simultaneously from the latter group (Williams 2012). Preovulatory follicles grow rapidly, partition centrally delivered resources, and eventually form an ovulation hierarchy as a result of resource partitioning and mutual inhibition (Fig. 1).

Two aspects of such organization make it amenable for evolution of environment-specific sex-biased order of ovulation.

First, all types of follicles are present in the ovary at the same time, and all aspects of recruitment, atresia, growth, and ovulation are regulated at the entire organismal level by just two key pituitary gonadotropins—follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Johnson 2000; Onagbesan et al. 2009). All follicles, therefore, are exposed to the same surges of these hormones, but these surges are converted to stage- and context-specific effects by conserved growth factors (Fig. 1). There are remarkably few of such growth factors, and they are re-used repeatedly in multiple contexts. For example, depending on location and timing, transforming growth factor- $\beta$  translates the same LH pulse that prevents atresia of small white follicles, stimulates growth, and prevents over-recruitment of small yellow follicles, keeps preovulatory follicles alive, and advances the sequence of ovulation (Johnson and Woods 2009; Onagbesan et al. 2009). Similarly, depending on the developmental stage, inhibin- $\beta$  regulates gaps in yolk membranes of white follicles (which leads to their recruitment), prevents differentiation of follicles, mediates formation of hierarchies in older oocytes, and finally, determines order of ovulation by translating a surge in LH, whereby it causes ovulation in the first follicle, but inhibits it in other follicles (Lovell et al. 2001, 2003; Yang et al. 2001; Johnson et al. 2005). Overall, once these growth factors are recruited in modular processes of oogenesis, they are rarely lost and instead are repeatedly co-opted for more functions with minimum embellishments (Fig. 1)—a central prerequisite for homeostatic hitchhiking.

Such co-option and modularity mean that the same phenotypic response can be accomplished by small changes in regulation of growth factors at different stages. For example, clutch size can be regulated by inhibin  $\alpha$  only hours prior to ovulation—a common method in poultry for terminating egg-laying (Moreau et al. 1998; Hoffman et al. 2007), and in response to factors that occur on the morning of egg-laying, such as dawn chorus, in wild birds. Yet, the same modifications in clutch size can be accomplished by regulation of early stages of oogenesis, such as limiting the number of recruited follicles at the onset of breeding season by insulin-like growth factor (IGF; Fig. 1). The same principle applies to other components of sex-biased sequence of egg-laying, such as sex-determination and order of ovulation—both can be affected by conserved growth factors at widely distinct stages of oogenesis

(reviewed by Rutkowska and Badyaev 2008). The crucial difference across these stages is their “environmental contingencies”—the predictability and repeatability of environmental variation that they experience. Some elements of this process experience the same environment during several generations, some over several years, and some only over a few hours (reviewed by Badyaev 2008). For example, small white follicles are the product of germ cells that are recruited from somatic tissues of epiblast when avian embryos are 14–16 h old—that is, 8–10 h before the eggs are laid. The movements and growth of these cells are guided not only by substances and molecules in maternal yolk, but also directly by the maternal environment (Fig. 1). On the other end of the time-arrow are environmental effects that are largely unique and unpredictable and that occur hours prior to final coordination of sex-determination, oocyte growth, and order of ovulation (Fig. 1). Such organization enables matching a complex adaptation to a particular environmental context—from highly recurrent, such as species-specificity and age-dependency of clutch sizes to novel features such as mate-quality, physiological condition, or changes in the weather. Thus, observing the recurrence of context in which we document sex-bias in order of egg-laying should be indicative as to which element of homeostasis is more likely to be associated with such bias.

## Empirical patterns

I will now examine predictions of the homeostatic hitchhiking perspective on evolution of sex-biased laying-order in the house finch (*Carpodacus mexicanus*)—the species that colonized most of North America from several introduced and naturally expanding populations.

### “Evolved adaptation” versus “phenotypic noise”:

#### Same mechanisms, but different sensitivity to context

We studied two house finch population—an ancestral (southern Arizona; hereafter sAZ) and a newly established (northern Montana; hereafter nMT). Both populations expressed strong sex-bias in order of egg-laying, but the environmental cues and adaptive consequences of this phenomenon were highly distinct between the two populations. In sAZ, sex-biased egg-laying is a highly evolved adaptation that is expressed seasonally in response to infestation of breeding females and their nests by the ectoparasitic nest mite *Pellonyssus reedi* (Badyaev et al. 2006b). This short-term annual infestation had strong effects on mortality of nestlings, particularly of males, and

during this time, breeding females strongly biased the order in which they produced sons and daughters—sons were produced later in the egg-laying sequence, they grew faster, and spent significantly less time in mite-infested nests compared with the mite-free period. Experiments show that this complex and precise adaptation can be induced in control females, and sex-bias in the order in which eggs were laid in this context was associated with female's allocation of hormones that facilitate ossification of long bones in embryos (R.L. Young and A.V. Badyaev, submitted for publication).

In contrast, in nMT, sex-biased laying-order is a passive consequence of early onset of incubation in the cold environment in which breeding females had to overlap incubation and oogenesis on days when ambient temperature was lower than could be tolerated by unattended eggs. Hormonal tradeoffs associated with such overlap were closely associated with sex-biased order of egg-laying that is produced under these circumstances (Badyaev et al. 2005). Such bias is especially pronounced in eggs from young females that breed under cold conditions for the first time; the sex-bias commonly disappears within 20–30 generations following establishment of the population in a novel environment.

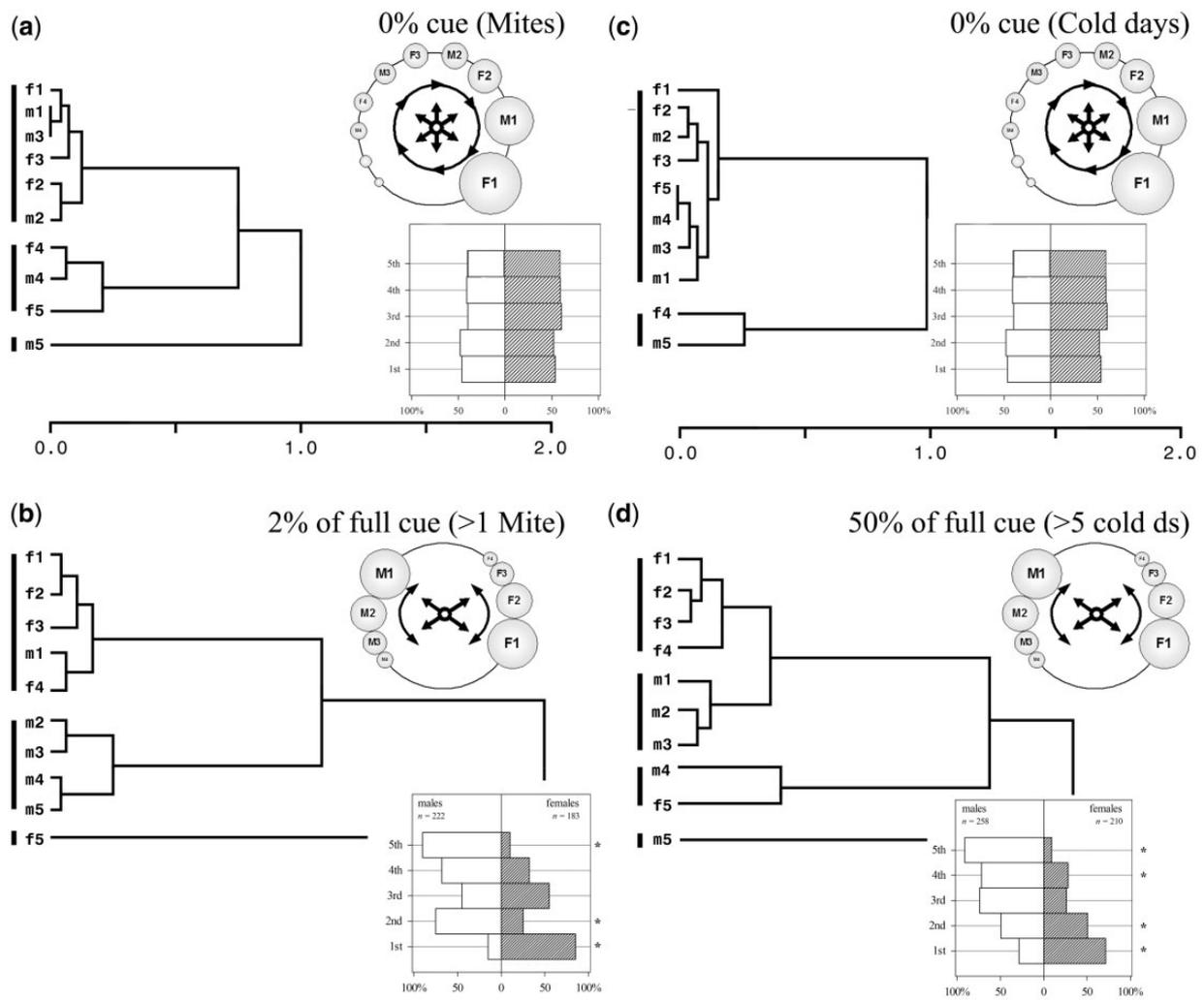
Thus, the same phenomenon of sex-biased order of egg-laying was expressed in two contexts: as a highly evolved adaptation and as “phenotypic noise.” We examined whether mechanisms behind these patterns were distinct between these contexts. To infer population-specific patterns of oogenesis in relation to sex-determination and ovulation-sequence (three components that together produce sex-biased laying-order), we combined data from direct measurements of oocyte growth obtained by yolk-staining with inference from accumulation of yolk substances with known timing of synthesis. If coordination between these three components is accomplished *de novo* under local selection, we expect to find variable proximate mechanisms between the contrasting contexts of “evolved adaptation” and “phenotypic noise.” However, if coordination between these components is preexisting or easily accomplished independently of external selection pressures, then we expect similar proximate mechanisms, but differences in evolved cue-recognition between the contexts.

We found strong evidence for the latter scenario. In both “evolved-adaptation” and “phenotypic-noise” contexts, expressed sex-biased order of laying was closely linked to the same mechanism—sex-specific temporal clustering of oocytes during development (Badyaev and Oh 2008). The precision of

such a mechanism and the extent of its expression did not differ between the contexts of “evolved adaptation” and “phenotypic noise.” Instead, what differed strongly was sensitivity to the environmental cue that was required for expression of sex-biased laying-order. Less than 2% of the “full cue” was required in the case of the “evolved adaptation,” and more than 50% of the full cue was required in the case of “phenotypic noise” (Fig. 2). Thus, coordination of oogenesis, sex-determination, and ovulation-order that produces sex-biased order of egg-laying in both contexts is accomplished readily under very different perturbations. However, sensitivity to the environmental cue, and, correspondingly, the expression of this pattern in the correct context, varied strongly between the two populations.

#### **“Phenotypic noise” is not random: Homeostatic selection on integration of oogenesis, sex-determination, and allocation of hormones**

To examine patterns of integration of sex-determination, oogenesis, and ovulation-order, we compared two additional house finch populations—in Alabama (hereafter AL) and northwestern Montana (hereafter nwMT)—that over 20–30 generations since establishment have evolved opposite patterns of sex-biased order of egg-laying (Badyaev et al. 2006a). Finches in both populations experience highly distinct relative humidity and temperature during the breeding season than existed at the site of their native population in Arizona, but have not had time to evolve distinct architecture of their egg shells (Stein and Badyaev 2011). Instead, distinct climatic conditions during breeding are accommodated by divergent incubation patterns with the end result of opposite patterns of sex-bias in relation to order of egg-laying—for example, in nwMT, females are produced in first-laid eggs and males in last-laid eggs, whereas the pattern is opposite in AL (Badyaev et al. 2003). Capitalizing on such contrast, we examined coordination of oocyte growth and substance-accumulation, sex-determination, and order of ovulation. We specifically focused on accumulation of steroids that are likely to have a sex-specific effect on development in a minority of oocytes in which combination of sex-determination and ovulation-order were reversed from the prevalent condition in a population, for example, males in first-egg positions in nwMT and females in last-egg positions in AL (Fig. 3). We found that such oocytes have highly unusual, and likely nonsurvivable, accumulations of steroids. For example, in nwMT, first-laid eggs that have male embryos have exceptionally

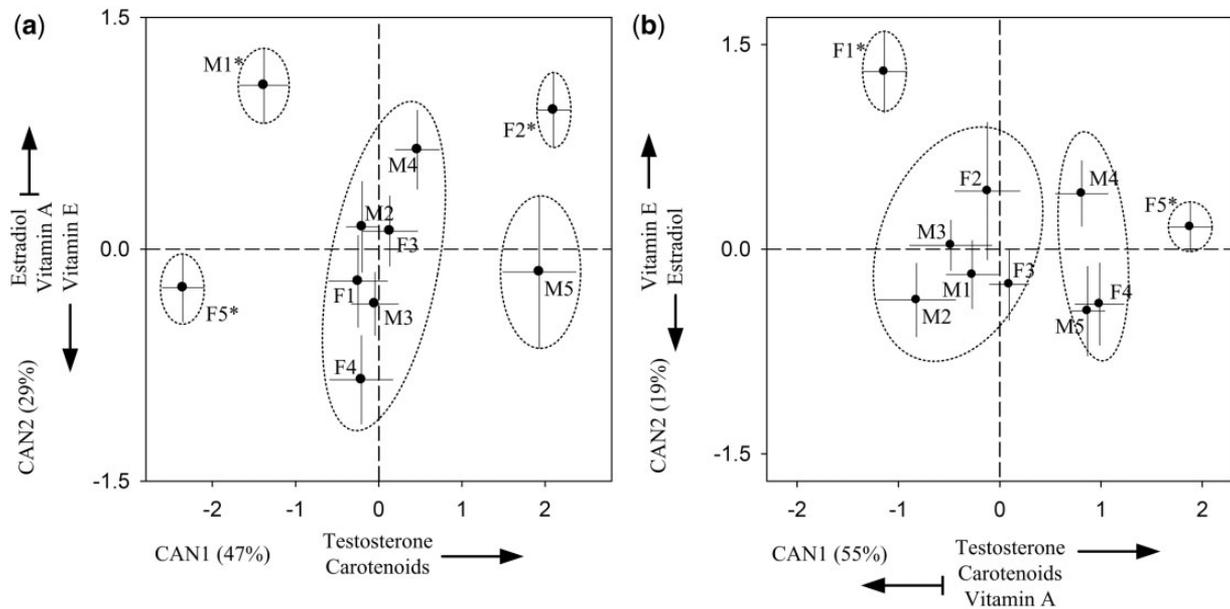


**Fig. 2** Sex-specific oocyte clustering during growth is closely associated with sex-biased order of egg-laying in first-breeding females in two distinct contexts (see text for details). An ancestral Arizona population (a) under control (mite-free) conditions, and (b) under seasonal mite infestation. A newly established nMT population, (c) under control ( $\leq 1$  “cold” days during oogenesis) conditions, and (d) at periods with  $>5$  “cold” days during oogenesis. Drawings show hypothetical arrangement of oocytes in the ovary that would correspond to sex-specific clusters or to a nonsex-specific hierarchical arrangement. Vertical bars on the left side delineate significantly distinct clusters. Modified from Badyaev et al. (2002, 2006b) and Badyaev and Oh (2008).

low concentrations of testosterone and high accumulations of estradiol (Fig. 3). The same pattern persisted for other egg-laying sequences in which the gender of the embryo was reversed in this, and other, populations (A. V. Badyaev, unpublished data). Thus, “incorrect” integration of sex-determination and hormone-allocation results in an accumulation of hormones that could be incompatible with normal sex-specific development. Importantly, even in the case in which sex-biased laying-order seems to be a passive outcome of females’ incubation strategies, as it is in these populations, homeostatic integration of ovulation-order, oogenesis, and sex-determination nevertheless produced a functional combination of sex-determination and

hormone-allocation, supporting the suggestion that these two processes can be linked regardless of their immediate consequences for fitness (Badyaev et al. 2008). Instead, subsequent natural selection, sorting among such “pre-made” configurations, can either eliminate them from a population or favor evolutionary retention of particularly beneficial matchings between sex-biased orders of egg-laying and environmental contexts.

Recognizing that different elements of oogenesis differ in contingency of interaction with the environment (e.g., from hours—in which all environmental influences are novel, to several generations, in which most environmental influences are predictable and recurrent; Fig. 1) would reveal which element of



**Fig. 3** Distinct acquisition and synthesis of testosterone, estradiol, carotenoids, and vitamins A and E in oocytes in which sex and ovulation-order are opposite of the prevalent patterns in a population (indicated by asterisks—e.g., male oocytes produced in strongly female-biased position and female oocytes produced in strongly male-biased positions). (a) Population from nwM and (b) population from AL. Shown are the means ( $\pm$ bivariate SE) of the first two canonical discriminant axes and percent of associated variance. Letters associated with numbers indicate sex (male or female) and ovulation-order (1–5). Dotted ellipsoids enclose groups of follicles not statistically different from each other. Modified from Badyaev et al. (2006a).

homeostasis is involved in the environmentally specific expression of sex-biased order of egg laying. The search for such elements can then be guided by empirical observations of timing of sex-biased order of egg laying in relation to external cues (such as in relation to changes in body condition, climate, or age).

## Acknowledgments

The author thanks Kristen Navara for organizing the symposium and anonymous reviewers for exceptionally insightful comments and suggestions.

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