



## Echoes of Early life: Recent Insights from Mathematical Modeling

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In the last decades, developmental origins of health and disease (DOHaD) has emerged as a central framework for studying early life effects, i.e., the effects of fetal and early postnatal experience on adult functioning. Apace with empirical progress, theoreticians have built mathematical models that provide novel insights for DOHaD. Here, we focus on three of these insights, which show the power of environmental noise (i.e., imperfect indicators of current and future conditions) in shaping development. Such noise can produce: (a) detrimental outcomes even in ontogenetically stable environments, (b) individual differences in sensitive periods, and (c) early life effects tailored to predicted future somatic states. We argue these insights extend DOHaD and offer new research directions.

*Keywords:* development; evolution; information; developmental mismatch; state-dependent modeling.

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### Introduction

The developmental origins of health and disease (DOHaD) framework is having interdisciplinary impact, inspiring research in diverse fields, such as medical and clinical science, developmental psychobiology, and public health. One influential hypothesis within DOHaD states that fetal and early postnatal experience prepare individuals for the environment they are likely to encounter in adulthood (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004, 2010; Gluckman et al., 2005, 2010). Such Predictive Adaptive Responses (PARs) are thought to be adaptive, if early and adult environmental conditions match (e.g., intrauterine under-nutrition reliably predicts famine in adulthood). If, however, conditions change during the lifetime, individuals might develop phenotypes that do not match their adult environment to some degree (developmental mismatch), which can produce detrimental outcomes, including impaired physical and mental health. We refer to this idea as the *PAR-mismatch hypothesis*. Although scholars who promote adaptive hypotheses in the DOHaD literature view phenotype-environment mismatch as one of several reasons why evolved mechanisms of plasticity may produce maladaptive outcomes (Conradt et al., in press; Hanson & Gluckman, 2014; Kuzawa & Quinn, 2009), it is a reason that is often given considerable explanatory prominence.

The best-known application of the PAR-mismatch hypothesis is the idea that intrauterine starvation prompts the development of altered insulin function and glucose metabolism (Barker, 1994). These changes can lead to diabetes and hypertension, and so are often seen as pathological. However, according to the PAR hypothesis, the negative effects are due not to the early conditions per se, but the mismatch between the early conditions and the later environment (in which, in affluent societies, resources are usually

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plentiful). The metabolic changes would actually be beneficial if individuals went on to experience chronic or temporary starvation in adulthood (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004, 2010; Gluckman et al., 2005, 2010). Consistent with this view are studies showing that the harmful effects of early starvation are in some cases attenuated or even absent if, matching early life conditions, the adult environment continues to be lacking in resources (e.g., Stanner et al., 1997; Stanner & Yudkin, 2001).

Another well-known application is the *Stress Inoculation Hypothesis* (Garmezy, 1991), which actually preceded the PAR-mismatch hypothesis in the DOHaD literature. This hypothesis proposes that exposure to mild stressors early in life prepares individuals to cope better with stressors later in life, and so these individuals have better outcomes than unprepared individuals, who are mismatched (Rutter, 1993). Consistent with this hypothesis are studies suggesting that adolescent rats exposed to social defeat are better able to cope with an aggressive male as adults than non-stressed controls (Buwalda et al., 2013; for a review of related results in mice, see Macrì et al., 2011). Similarly, squirrel monkeys who experienced brief separations from their mothers as infants were better able to cope with separations later in life than controls (Lyons et al., 2009). And a recent study in humans suggests that immigrant children born to expatriates are less likely to develop affective, personality, and substance use disorders than other immigrant groups (Cantor-Graae & Pedersen, 2013; Nederhof, 2013). A caveat is that studies of stress inoculation typically define 'better coping' in terms of health and well-being, rather than fitness, the true currency of natural selection (Belsky, 2008; Ellis et al., 2012; Frankenhuis & Del Giudice, 2012).

Mismatch between early and later environmental conditions has also been

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implicated in the development of cognitive and socio-emotional abilities in children and adolescents (Frankenhuis & Del Giudice, 2012; Glover, 2011; Glynn & Sandman, 2011; Nederhof & Schmidt, 2012). There are few studies, but initial findings are remarkable. In a recent article titled *Prescient Human Fetuses Thrive*, Sandman and colleagues (2012) report that infants who experience congruent levels of maternal depression before and after birth (high or low levels) show superior motor and mental development in their first year, compared with infants who experience incongruent levels of maternal depression (low prenatal and high postnatal levels, or vice versa). These authors argue that already inside the womb, infants start tailoring their brains and bodies to future conditions and benefit if their prenatal and postnatal environment match, even if both are stressful (for related research on non-human animals, see Schmidt, 2011; Homberg, 2012). In short, some findings on metabolism and cognitive and socio-emotional outcomes support what Gluckman and Hanson (2010) have described, perhaps prematurely, as “the emerging consensus”: harmful effects reflect “the maladaptive consequences of developmental plasticity, arising from discordance between the triggering and later environments” (p. 21).

The goal of this paper is to extend and challenge this emerging consensus based on three insights provided by recent mathematical modeling. All three of these insights demonstrate the power of *environmental noise* (i.e., imperfect indicators of current and future conditions) in shaping development. The models we discuss explore two sources of environmental noise. First, organisms do not have direct access to the statistics (or *states*) of their environments (e.g., the level of danger). Rather, they may estimate (or ‘infer’; no conscious process implied) these states based on *cues*, i.e., observations that

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are more likely to occur in certain states of the world than in others. Second, the current state of the world is probabilistically correlated with future states of the world. So, even if our estimate of today is correct and precise, we can only make informed guesses about tomorrow, as in weather forecasting. Evolutionary models of development tend to ignore perceptual noise; they assume that individuals make accurate observations (e.g., detecting an angry face). Instead, they focus on the challenges of using these observations to infer the present state of the environment (e.g., the current level of danger) and predict future environmental states (e.g., future levels of danger).

All models are by design simplified versions of reality that capture only some essential components of a process or system (Frankenhuis et al., 2013; Frankenhuis & Tiokhin, 2018; Houston & McNamara, 1999; Levins, 1966; Mangel & Clark, 1988). Each model makes particular assumptions, which may be criticized. The models we discuss, for instance, assume that natural selection has perfectly adapted developmental systems to their environment (this does not imply that every individual is optimally adapted; see below). This *phenotypic gambit* (Grafen, 1984) allows researchers to ignore matters of genetic and physiological instantiation (Maynard Smith et al., 1985). The gambit is a methodological stance that provides a starting point for research. If observations contradict model predictions, we need to refine our model. Statistician George Box (1976) famously remarked that all models are wrong but some are useful. Simple models can be extremely useful because they increase precision, make assumptions clear and explicit, remove ambiguities from natural language, ensure logical consistency in argumentation, generate novel predictions, and provide a better understanding of complex interactions that are impossible to intuit without the help of

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formalizations. The utility of any particular model will depend, of course, on the assumptions it makes and how well it is constructed and analyzed. And, all models are limited. It is key to understand and acknowledge what a model can tell us and what it cannot.

### **Modeling development**

All traits of organisms (phenotypes) result from development, i.e., are the product of a process that begins with the zygote and proceeds during the subsequent lifetime. Hence natural selection can only modify phenotypes by shaping *developmental systems*, i.e., the array of factors (e.g., genes) and processes (e.g., gene regulation) that give rise to phenotypes (Bjorklund et al., 2007; Dall et al., 2015; Frankenhuis et al., 2013; Mangel & Ludwig, 1992; McNamara et al., 2016; West-Eberhard, 2003). Natural selection favors systems that tend to construct *adaptive* phenotypes, which increase fitness. The term *fitness* is often used to denote individual survival and reproduction. However, fitness should actually be assigned to developmental systems (or strategies, genotypes), not to individuals, and the appropriate measure of fitness depends on the environmental context and species. The distinction between developmental systems and individuals is crucial because, as we will see, optimal systems often produce detrimental outcomes for some individuals (Frankenhuis & Del Giudice, 2012).

Individuals change over time, depending on influences internal (e.g., glucose levels) and external to the body envelope (e.g., resources in the environment). Models describe such changes using *state variables*, which quantify the current state of the individual and predict its future state, if only probabilistically. State variables can represent any factor of interest. For example, a model of growth might describe the

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composition of the body using variables representing skeletal size, bone density, muscle mass, fat levels, the types of tissues present and their degree of differentiation, patterns of gene methylation, brain wiring, hormone levels, receptor densities, etc. Each variable takes on a specific value, which might change over time. Age is typically not a state but rather a crude aggregate measure, because individuals of the same age might be in different developmental and physiological states.

Developmental models require an *initial state*, which depends on the research question. For models of epigenetics, the initial state could specify which genes are methylated or hormone levels inherited from parents; for models of social learning, an individual's knowledge before any social interactions have occurred. State changes occur throughout the lifetime, but early changes are often the most important as these have lifelong effects. To understand the fitness consequences of early developmental responses, it is necessary to take later effects into account. For instance, chronic activation of stress responses early in life might increase immediate survival (by protecting against threat), but may also accelerate telomere attrition and associated aging, reducing fecundity later in life (Herborn et al., 2014; Metcalfe & Monaghan, 2001).

Models describe developmental processes by changes in the values of state variables. Because development in real organisms is multifactorial (i.e., it depends on the interactions between many different factors and processes), and small differences in these factors and processes can affect outcomes, development is often modeled as a *stochastic process*; i.e., the transitions between states are probabilistic, yet certain outcomes might be more likely than others. Even if we know an organism's current state, we cannot predict its next state with certainty. Some sources of stochasticity are internal. If an

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animal ingests food, it burns some fraction, stores another, and excretes the remainder. We can predict patterns (e.g., store more if winter is coming), but not exact amounts, because “cellular metabolism is inherently stochastic, and a generic source of phenotypic heterogeneity” (Kiviet et al., 2014, p. 376). Other sources are external. If an animal forages, it might find food, encounter a mate, contract disease, be predated on, or be killed by a rival. The probabilities of these different outcomes depend on the animal’s foraging behavior (e.g., hunting for large rewards in an open field, or for small rewards in a safer refuge), which in turn depends on its state (e.g., hunger level, calories needed to survive the night, migration, or hibernation). Despite stochastic influences, state changes are not completely at random. The probability that a given change in state will occur (e.g., energy increase) depends on interactions between the environment (e.g., food availability, density of predators) and the developmental system (e.g., behavior, metabolic efficiency).

Animals typically attempt to increase their knowledge about the environment to respond to it appropriately (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). In particular, an animal might use cues, that is, observations that provide *information* (reduce uncertainty) about some relevant dimension, to improve its estimate of the current conditions (e.g., dead conspecifics indicate predators). An animal might also estimate future conditions, forecasting the future over the timescale of hours (e.g., barometric changes predict thunderstorms), seasons (e.g., a mild winter predicts a mild summer), or even generations (e.g., current abundance predicts adequate nutrition for future offspring) (Botero, Weissing, Wright, & Rubenstein, 2015). Cues are often

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imperfect: they reduce uncertainty, but do not eliminate it. Moreover, individuals are likely to sample different cues, resulting in estimates that diverge even for individuals in the same environment, which might produce variation in phenotypes (Fischer et al., 2014; Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016). Animals also use social cues (Taborsky, 2017). A potential mate might show courtship cues, which probabilistically predict its willingness to have sex. A rival might show threat signals, which predict its ability to fight. On both immediate and developmental timescales, organisms are continually making consequential decisions under uncertainty in an ever-changing world.

So, what might a model look like? We may be interested in the question whether it is biologically adaptive to mature earlier in a high-mortality environment (Belsky et al., 1991; Ellis, 2004; Nettle et al., 2013). To study this question, we can build a model examining when it is adaptive for developmental systems to accelerate their rate of maturation based on early life experiences versus mature at a fixed rate (i.e., irrespective of experience)? The answer will depend on the environment. We can, for instance, imagine an environment that fluctuates between different states (e.g., safe or dangerous) during the lifetime of an individual. These states are auto-correlated over time; i.e., this year's level of mortality predicts next year's level, but not perfectly. We may then use an optimization technique to compute optimal developmental strategies, which specify the best decision for every possible state of the developmental system. This analysis might show that if only auto-correlation is very high, early life experience tends to provide an accurate forecast of adult conditions; and hence, individuals should use it. By contrast, if auto-correlation is moderate or low, early life experience provides a poor forecast of adult

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conditions and might actually be misleading. In that case, developmental systems might do better by maturing at a fixed rate that is adapted to the average level of mortality over evolutionary time (Nettle et al., 2013). This result is theoretically interesting because it contradicts the intuition that as long as there is *some* auto-correlation in the environment, it is adaptive to tailor developmental trajectories based on early life experience.

Empirically, it highlights the importance of actually measuring the statistics of environments (which is rarely done in current research) in order to assess the plausibility of evolutionary explanations, such as the PAR-mismatch hypothesis.

### **Detrimental outcomes in a stable environment**

The PAR-mismatch hypothesis regards developmental mismatch as a key source of departure from optimal health and wellbeing. Such mismatches result from changing conditions over the course of ontogeny (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004, 2010; Gluckman et al., 2005, 2010). The PAR hypothesis guides much empirical research on early life effects and has been incorporated into several influential theoretical frameworks in psychology. (Please note that we use the term *early life effects*, rather than *developmental programming*, in order to avoid a deterministic connotation. Early-life experience may have a lasting impact on adult traits, even if these traits continue to exhibit some degree of plasticity; Takesian & Hensch, 2013).

To illustrate, the theory of Biological Sensitivity to Context (Boyce et al., 1995; Boyce & Ellis, 2005) proposes that individuals evolved to tailor their levels of plasticity to expected future conditions, with the potential for developmental mismatch being a cost of increasing levels of plasticity (Del Giudice & Ellis, 2016; Ellis et al., 2011). The Bet-hedging Hypothesis of Differential Susceptibility (Belsky, 1997) states that it is adaptive

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for parents to produce offspring with varying levels of plasticity, based on the idea that plastic offspring thrive when current cues correctly prepare them for future conditions, but suffer when current cues provide an unreliable forecast (e.g., when a child socially learns outdated knowledge and behavior from its caregivers), resulting in developmental mismatch; hence, the argument goes, parents produce less plastic offspring as well, which are less affected by current cues (Belsky, 2005; Belsky & Pluess, 2009; Ellis et al., 2011; for a model, see Frankenhuis et al., 2016). The Adaptive Calibration Model (Del Giudice et al., 2011) posits that early life experience *calibrates* the stress response system and life history strategies (e.g., the timing of puberty) to the challenges an individual is likely to encounter during its lifetime, which is thought to be adaptive on average, but may result in health costs if later conditions differ substantially from earlier conditions (e.g., when a child develops in a dangerous and unpredictable neighborhood or family and then moves into a safe and supportive school, yet continues to use coercive behavioral strategies that worked well in its initial environment to accomplish goals, which might result in peer rejection, which in turn could produce physical and mental health problems).

We agree that developmental mismatch can result from changing conditions over ontogeny. However, even evolutionary developmental psychologists often overlook that inferring the present state of the world poses challenges for organisms, just as predicting future conditions does. The present conditions do not automatically ‘get under the skin’ or become ‘biologically embedded’ with perfect accuracy. *State-dependent optimality modeling* is a suitable method that is used in biology to determine adaptive decisions in a particular environment, when decisions are interdependent over time, meaning that past decisions affect future options (Houston & McNamara, 1999; Mangel & Clark, 1988; for

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explanation tailored to psychologists, see Frankenhuis et al., 2013, 2018). Such modeling clearly shows that even if an environment is completely stable within lifetimes, noisy environmental cues often produce substantial mismatch between some individuals' phenotypes and actual conditions (Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016; Meacham & Bergstrom, 2016). Such mismatch even occurs when individuals: (a) have the opportunity to repeatedly sample cues, (b) obtain cues at no cost throughout their entire lifetimes, and (c) there is a cost to being mismatched. These mismatches do not result from malfunction; rather, they are produced by a developmental system responding optimally to noisy inputs in a context it is evolutionarily adapted to.

To illustrate, an optimal decision rule can produce excessive anxiety in some individuals in a stable, safe environment (Meacham & Bergstrom, 2016). Consider agents that have opportunities that are either profitable or dangerous. Before pursuing or declining an opportunity, an agent samples a cue informative about the level of environmental danger. Next, an agent chooses to pursue or decline, following the optimal decision rule (which maximizes its expected fitness). If an agent pursues, there is a good or bad outcome, and an agent gains additional information about the level of danger. If an agent declines, however, it does not gain further information (e.g., a rabbit leaving its burrow in order to forage learns more about the environment than one that remains in its burrow). Because cues are stochastic, some individuals sample more danger cues than others before making decisions. These individuals may set their sensitivity to threat higher than necessary, becoming overly anxious. Their anxiety, in turn, leads them to decline opportunities, preventing them from learning the environment is actually safe. Accordingly, the model "predicts that disorders of excess anxiety will be

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common but disorders of insufficient anxiety will be rare” (Bergstrom & Meacham, 2016, p. 216; for related signal detection models exploring the evolutionary origins of mood disorders, see Bateson et al., 2011; Nettle & Bateson, 2012; for a model showing that depression can result from following an optimal decision rule in a changing environment, see Trimmer et al., 2015).

Mathematical models generally show that developmental mismatch is more likely to occur when systems have been exposed to greater environmental variability over evolutionary time (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). A system that has evolved in a variable environment is uncertain about the conditions early in ontogeny. Models represent the distribution of environmental states experienced by a species as a prior probability distribution (*a priori*). If a species experienced a narrow range of environmental states, the prior is centered on those states, and the system starts out with a good estimate, if the current environment is still within the range the system has evolved in. By contrast, if a species experienced a wider range, the prior is more dispersed, and so it will be more challenging for the developmental system to match phenotypes to current conditions. Note, however, that if an environmental state is truly novel, meaning it has never occurred before in a species’ evolutionary history, developing individuals should assign zero probability to it, irrespective of the shape of their priors. Hence, it is challenging if not impossible to model responses to completely novel environments within a Bayesian framework (for discussion of the applications and limitations of the Bayesian optimality models, see Bowers & Davis, 2012; Gopnik & Bonawitz, 2015; Griffiths et al., 2010; Mangel, 1990; Ramírez & Marshall, 2017; Trimmer et al., 2012).

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Mismatch is also likely when systems only have access to low-reliability cues, as these cues help little in discriminating between different environmental states (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). When cue reliability is very low, organisms might ignore cues altogether, and evolve non-plastic strategies, such as diversified bet-hedging, producing fixed offspring of different types, guaranteeing that some fraction of them will match the current environmental state (Donaldson-Matasci, Lachmann, & Bergstrom, 2008; Frankenhuis et al., 2016; Leimar, Hammerstein, & Van Dooren, 2006; McNamara et al., 2016; Seger & Brockmann, 1987). Such bet-hedging illustrates a point we made earlier: fitness should be assigned to strategies, not to individuals. Natural selection might result in strategies that produce detrimental outcomes for some individuals.

Even systems that do have access to moderate-reliability cues, however, might produce some individuals that are substantially mismatched. Such mismatch is likely to occur when it is adaptive to commit to a developmental trajectory early in life, even if doing so implies having had few opportunities to learn about the environmental state, thus increasing the risk of mismatch. Committing early might be favored, for example, when it takes time to build conditional adaptations (e.g., predator defenses) that yield high fitness in specialized form, if they are well matched (Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016). A general lesson is that natural selection maximizes the fitness of developmental systems (not of individuals), and these systems are likely to produce some mismatched individuals, even when these systems function optimally in a context they are evolutionarily adapted to.

### **Variation in plasticity between and within individuals**

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Why do some adopted children adapt swiftly to their new environment, while others remain burdened by their difficult past? And, why do different mental systems within these children adapt at different rates to new conditions (Zeanah et al., 2011)?

Biologists have wondered why all organisms are not Darwinian demons, i.e., why they are unable to always perfectly match their brains, bodies, and behavior to the current conditions. Of course, organisms do retain some degree of plasticity in many traits and behaviors throughout their lifetimes. This degree of plasticity, however, tends to change (increase or decrease) over the life course, and individuals differ in their trajectories of change. The term 'sensitive periods' describes periods or states in which experience shapes a given trait or behavior to a larger extent than other periods or states (Fawcett & Frankenhuis, 2015). Importantly, sensitive periods do not imply 'critical periods', in which the impact of experience is limited only to a particular period or state, with irreversible effects (Takesian & Hensch, 2013). Recent mathematical modeling shows that optimal developmental systems may produce species-typical sensitive periods in development as well as individual differences in sensitive periods, even in environments that are stable within lifetimes (Fawcett & Frankenhuis, 2015; Frankenhuis & Fraley, 2017). There are several reasons for this variation.

Individuals might start out with different priors because they have inherited different information from their distant ancestors (e.g., via genes) or from their immediate ancestors (e.g., via parental effects or inherited epigenetic factors) (Dall et al., 2015; Jablonka, Oborny, Molnár, Kisdi, Hofbauer et al., 1995; Hanson & Gluckman, 2014; Kuzawa, 2005; Lachmann & Jablonka, 1996; Marshall & Uller, 2007; McNamara et al., 2006; Stamps & Krishnan, 2014; Stamps & Frankenhuis, 2016; Trimmer et al.,

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2011; Uller, 2008; Uller, English, & Pen, 2015). Priors can differ in their means and variances. Individuals whose ancestors have been exposed to higher levels of harshness (e.g., war, famine) might take longer to adjust to beneficial conditions, as their personal experience is more discrepant with inherited information. Individuals whose ancestors have been exposed to greater environmental variability might adjust more flexibly when their experience is discrepant with inherited information, because their priors are more dispersed. The extent to which experience (e.g., adversity) affects individuals at some life stage thus depends partly on their inherited priors.

Individuals might sample cues of different reliabilities. The reliability of a cue depends on its likelihood of occurring in different states of the environment. A cue is more reliable to the extent that it is differentially likely to occur in different states of the world, thus allowing for discrimination between these states (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). For example, a child who observes that her entire community suffers from death and disability can draw a stronger inference about environmental conditions (i.e., conditions are harsh) than a child who occasionally observes a little suffering in some adults. The reason is that widespread and severe suffering is unlikely to happen except when conditions are harsh, whereas some occasional suffering could happen even in beneficial conditions, if there is a streak of bad luck due to chance (e.g., minor injuries happening to different people in the same village). Children experiencing more reliable cues might reduce their uncertainty about environmental conditions faster, reducing their plasticity earlier in life than children experiencing less reliable cues (Frankenhuis & Panchanathan, 2011; Panchanathan &

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Frankenhuis, 2016). The ‘reliability’ of cues (the extent to which the frequency of a cue varies between different states of the environment) should be distinguished from their ‘information value’ (the extent to which they reduce uncertainty; this depends both on the cue reliability and on current knowledge) and their ‘fitness value’ (the extent to which optimal use of the cue increases fitness; Donaldson-Matasci, Bergstrom, & Lachmann, 2010; McNamara & Dall, 2010; Pike, McNamara, & Houston, 2016). Moreover, the extent to which organisms can discriminate between different environmental states depends both on the cue reliability and on the ability of sensory systems to accurately perceive cues. Discrimination is a product of cue reliability discounted by perceptual inaccuracy.

Even when classes of cues are reliable and well perceived, individuals might receive misleading instances of those cues, by chance variation akin to sampling variation in classical statistics. This will result in estimates that diverge between individuals in the same environment, which affect the retention and decline of plasticity (Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016). As cues are noisy, some individuals will have more consistent experiences than others (e.g., all safe cues vs. some safe and some danger cues). Mathematical models show that individuals who have more consistent experiences reduce their uncertainty at faster rates, hence may lose their plasticity earlier in their lives, even to the point of irreversibility, i.e., critical periods (Fawcett & Frankenhuis, 2015; Frankenhuis & Fraley, 2017). For example, when two people live in an affluent neighborhood in which robberies rarely occur, one might be victimized twice, the other never. As both have beneficial experiences as well, the victim overall has more heterogeneous experiences (some good and some bad ones). Hence,

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this individual might retain more plasticity for longer, adjusting more easily to harsher conditions if their environment changes.

In addition to the variation in priors, cue reliabilities, and stochasticity in cues, mathematical models also suggest other factors that should affect the retention and decline of plasticity over the life course. These factors include developmental variation in: (a) the availability of cues, (b) the fitness benefits of information, and (c) the fitness costs of plasticity (Fawcett & Frankenhuis, 2015). The crucial point for now is that inferring the present state of the world poses challenges for organisms, just as predicting future conditions does, and responses to these challenges may help to explain individual differences in early life effects observed in empirical studies.

### **Predicting future somatic states**

A researcher who documents an early life effect might be tempted to infer that the effect evolved in an environment that was stable within individual lifetimes; why else would the organism rely on early experience in setting adult phenotype? This inference, however, is not necessarily warranted. Mathematical models show that there are at least two distinct, but mutually compatible, adaptive reasons for the evolution of early life effects: external and internal Predictive Adaptive Responses (PARs; Nettle et al., 2013; Rickard et al., 2014; Wells, 2012, p. 262, suggests a similar distinction).

The external PAR account proposes that some early life effects *have evolved in response* to factors in the external environment (e.g., intrauterine under-nutrition) that forecasted future environmental conditions (e.g., famine in adulthood) (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2010). On this view: “the organism presets its physiology in expectation of that physiology matching its future environment. PARs,

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therefore, are a form of phenotypic plasticity in which the resulting phenotype is not necessarily advantageous in the environment concurrent with or immediately following the inducing cue, but is likely to be advantageous in an anticipated future environment. The cue thus acts as a predictor of the nature of this environment” (Gluckman et al., 2005, p. 527).

The internal PAR account, in contrast, proposes that early life effects *have evolved because* early experience alters future life prospects by having irreversible effects on future bodily states (e.g., through limiting growth, increasing oxidative stress, or accelerating telomere attrition) (Figure 1). Such limitation brings about a correlation between early experience and adult prospects, irrespective of future environmental conditions (Nettle et al., 2013; Rickard et al., 2014). Internal PARs are more than developmental constraints (Lea, Altmann, Alberts, & Tung, 2015); they are adaptive responses to such constraints that tailor individuals to their predicted somatic futures. Crucially, the internal-external PAR distinction exists at an ultimate level of explanation (evolutionary history and adaptive value), and not at a proximate level (developmental and physiological processes). At a proximate level, all PARs are mediated by somatic processes, and these processes may or may not be similar for different PARs (for discussion of differential predictions at a proximate level, see Rickard et al., 2014).

[ INSERT FIGURE 1 ABOUT HERE ]

Mathematical models show that external and internal PARs can both evolve, but do so in different conditions (Nettle et al., 2013; Del Giudice, 2014). Natural selection

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favors external PARs only when environmental conditions are stable over individuals' lifetimes (e.g., if the world is harsh today, it will likely be harsh next year). Internal PARs do not require such stability; rather, these require that individuals' somatic conditions are stable over their lifetimes (e.g., if my body was fragile this year, it will likely be fragile next year) (Figure 1). If an environment is completely unpredictable, natural selection does not favor external PARs, but it is likely to favor internal PARs, if earlier somatic states are correlated with later ones. Such somatic autocorrelation exists in many species. For instance, telomeres, the protective 'caps' on the end of chromosomes, are considered markers of life's insults (Blackburn et al. 2015), in that they are affected by a variety of exposures to stress and adversity. Telomeres shortened in early life tend to remain short for the rest of life, and telomere length appears to be a good predictor of future health and longevity in humans (Bakaysa et al., 2007; Kimura et al., 2008; Njajou et al., 2009). The most compelling cases for external PARs have been documented in organisms that are short-lived and/or sessile, in which there is not much scope for the environment to change in between the receipt of early cues and the environment of selection, such as certain species of fungi (Markiewicz-Potoczny & Lydall, 2016), plants (Galloway & Etterson, 2007), and crickets (Storm & Lima, 2010). Studies in humans, however, suggest that having a good start in life (a *silver spoon*) improves fitness more than matching environmental conditions early and later in life (e.g., Hayward & Lummaa, 2013; Hayward et al., 2013; Wells, 2007; Wells & Johnstone, 2017). Perhaps this is because humans are long-lived, like the macaques and reindeer, to which we turn next.

Recent studies suggest the existence of internal PARs in wild long-lived animals

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that inhabit ecologies that might be too unpredictable for external PARs to evolve. For instance, Assamese macaque (*Macaca assamensis*) that inhabit Southeast Asian forests experience highly unpredictable environmental conditions: the year-to-year predictability of food abundance and rainfall is very low, so that it is not possible to use early life cues to predict later environmental conditions. Nonetheless, in this species, offspring whose energy intake is reduced early in life as a result of their mother's physiological stress display accelerated growth, consistent with their pursuing a fast life-history strategy (Berghänel et al., 2016). Similarly, living at high latitudes, Svalbard reindeer (*Rangifer tarandus platyrhynchus*) experience major variation in resources in the winter due to variation in rain-on-snow events, which create ice layers on the ground or in the snow that limit access to vegetation. Female reindeer that experienced many rain-on-snow events in utero tend to be relatively light and small during both the juvenile and adult stages. Despite this somatic disadvantage, these females attain reproductive success in the first six years of their lives comparable to females of higher somatic quality, who had better access to vegetation early in ontogeny. Their rough start in early life manifested only among females aged 7 years and older, who had lower annual reproductive success. The females of lower-somatic quality engaged in reproductive events at a lower body mass than females of higher-somatic quality. This increased investment in reproduction probably evolved not as a response to predicted future environmental conditions, but rather as a response anticipating accelerated somatic decline (Douhard et al., 2016).

Studies of human development show correlations between early somatic state and later phenotypic outcomes, even if early somatic state is not correlated with early environmental stress, or after controlling for such stress. For example, British girls who

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experienced chronic disease in childhood develop earlier timing of first reproduction, even if chronic disease is not correlated with environmental stress, such as father absence and socioeconomic status (Waynforth, 2012; see also Hill et al., 2016; Valencia & Cromer, 2000). Similarly, Danish data show that low birth weight in girls and boys predicts lower levels of trust in adulthood, even after controlling for childhood family environment. Low birth weight predicts small body size and physical vulnerability later in life, which might increase the risk of being socially exploited, making vigilance adaptive (Petersen & Aarøe, 2015). A longitudinal study in the US supports both the internal and external PAR hypotheses. It shows that even after controlling for internal health, early-life adversity predicts greater adolescent risk-taking, problematic functioning, and earlier age of menarche (for girls); and, internal health mediated the relation between the early environment and adolescent behavior (Hartman et al., 2017; see also Chua et al., 2017). This finding highlights the fact that the internal and external PAR accounts are mutually compatible: individuals might tailor their development to predicted future environmental states as well as future somatic states.

### **Implications for DoHaD**

We have argued that environmental noise has the potential to: (a) produce detrimental outcomes for some individuals, even for an optimally functioning system in a stable environment, (b) cause individual differences in the timing and reversibility of sensitive periods, and (c) favor early life effects tailored to predicted future somatic states, instead of or as well as predicted future environmental states. We conclude with a brief discussion of the implications for DoHaD.

The first implication is that is important to explicitly incorporate noise in theory

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development. That is, models of the evolution of developmental systems cannot simply assume that individuals know environmental conditions perfectly, or that every individual experiences the average environment. Rather, techniques such as stochastic dynamic programming are required (Frankenhuis et al., 2018; Houston & McNamara, 1999; Mangel & Clark, 1988), which explicitly incorporate the fact that average properties of environments lead to probability distributions of experience, with different individuals receiving different sequences of experience as a matter of course.

Second, a general implication of the material reviewed is that the normal outcome of evolved developmental systems is a great degree of variation, both in final phenotype, and in the timing of the phenotype's development (Holmes & Patrick, 2018). Extensive variation emerges even if the developmental system is operating normally; i.e., if there is no 'pathology' in the strict sense (Cosmides & Tooby, 1999; Wakefield, 1992, 1999; for recent discussion, see Griffiths & Matthewson, 2016; Matthewson & Griffiths, 2017). DoHaD has also tended to focus particularly on mismatch between early developmental and adult conditions as a source of deleterious phenotypes. However, as we have argued, a certain fraction of the population should be expected to show deleterious phenotypes even when there is no such mismatch. Essentially, noise requires us to shift focus from the expectation that *individuals* will be optimally adapted to their environment (if there is no pathology or environmental change). Instead, developmental *systems* are the outcome of adaptive evolution, and systems, through their interactions with noisy environments, produce clouds of phenotypic variation at the individual level (Barrett, 2015). Many of those individuals survive and reproduce successfully (otherwise the system could not persist), but not all will do so.

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Thus, when explaining disease states from an evolutionary perspective, we cannot, without further evidence, make strong inferences that the cause is mismatch between developmental and adult environments. More positively, techniques such as stochastic dynamic programming allow us to build sophisticated models of developmental systems from which the consequences of different kinds of environmental change and developmental input can be simulated. These predictions are at the level of phenotypic distributions, not individual phenotypes, and so they have considerable empirical relevance to the changing population burden of health and disease. For example, dynamic models predict that the distribution of body fat stores will be affected by (imperfect) cues of food scarcity, and will under many conditions contain more individuals with excess fat than with insufficient fat, because of the historical strength of selection on avoiding starvation (Higginson, McNamara, & Houston 2016; Higginson & McNamara 2016). This prediction may help explain why the prevalence of obesity can be, apparently paradoxically, increased rather than decreased by food insecurity and restrictive dieting (see also Nettle, Andrews, & Bateson 2017).

A third implication is that longitudinal studies are important (Clutton-Brock & Sheldon, 2010), because early experience should strongly affect later development, in complex and path-dependent ways. This premise has always been a strength of DoHaD. We note in particular the potential relevance of longitudinal studies of wild-type animals under ecologically realistic conditions. Using inbred model strains under standardized developmental conditions is generally favoured in biomedical science, for reasons of experimental control, but it may lead to quite unrealistic expectations about the degree of phenotypic variability that is the normal outcome of development. Having said this, even

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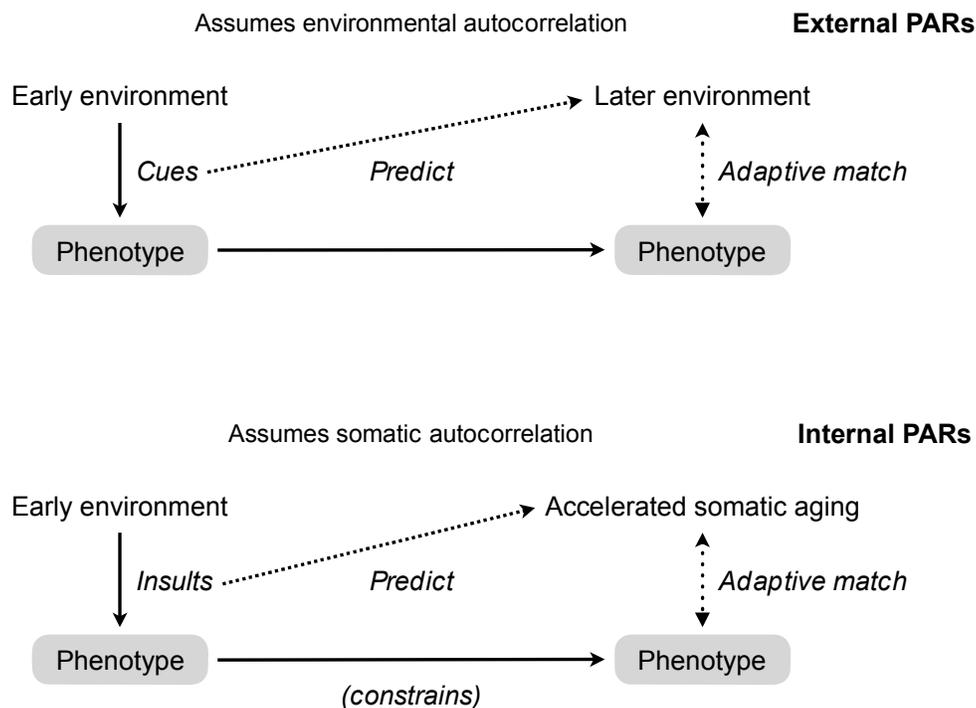
with inbred strains and standardized conditions, a great degree of phenotypic variability is in fact observed (Freund et al., 2013; Lynch & Kemp, 2014).

Finally, although adaptive hypotheses about early life effects focus on explaining general phenotypic tendencies that emerge in the normal range of environments, formal modeling of these hypotheses does invite further reflection on the distinction between statistical rarity and pathology. Given that the distribution of environmental experiences is probabilistic, and phenotypic development is affected by noise, then extreme phenotypic states will occur with a low frequency in all populations of normally functioning animals. Thus, discovering a state of an organ or system that is rare does not necessarily mean that the system is pathological, in the sense of lesioned or subject to a large deleterious genetic mutation. Rather, the individual may just have had an unlikely sequence of developmental inputs. They may be at the edge of the normal cloud.

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**Figure 1 and caption**

The distinction between internal and external PARs: two distinct, but mutually compatible, adaptive reasons for the evolution of early life effects. Whereas external PARs require environmental autocorrelation, internal PARs depend on somatic autocorrelation. Internal PARs can evolve even when environmental autocorrelation is low; external PARs cannot, because it is impossible to forecast future environmental states and adapt to them (Nettle et al., 2013; Rickard et al., 2014). Note: internal PARs are more than developmental constraints; they are adaptive responses to such constraints that tailor individuals to their predicted somatic futures.



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**Echoes of Early life: Recent Insights from Mathematical Modeling****Abstract**

In the last decades, developmental origins of health and disease (DOHaD) has emerged as a central framework for studying early life effects, i.e., the effects of fetal and early postnatal experience on adult functioning. Apace with empirical progress, theoreticians have built mathematical models that provide novel insights for DOHaD. Here, we focus on three of these insights, which show the power of environmental noise (i.e., imperfect indicators of current and future conditions) in shaping development. Such noise can produce: (a) detrimental outcomes even in ontogenetically stable environments, (b) individual differences in sensitive periods, and (c) early life effects tailored to predicted future somatic states. We argue these insights extend DOHaD and offer new research directions.

*Keywords:* development; evolution; information; developmental mismatch; state-dependent modeling.

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**Introduction**

The developmental origins of health and disease (DOHaD) framework is having interdisciplinary impact, inspiring research in diverse fields, such as medical and clinical science, developmental psychobiology, and public health. One influential hypothesis within DOHaD states that fetal and early postnatal experience prepare individuals for the environment they are likely to encounter in adulthood (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004, 2010; Gluckman et al., 2005, 2010). Such Predictive Adaptive Responses (PARs) are thought to be adaptive, if early and adult environmental conditions match (e.g., intrauterine under-nutrition reliably predicts famine in adulthood). If, however, conditions change during the lifetime, individuals might develop phenotypes that do not match their adult environment to some degree (developmental mismatch), which can produce detrimental outcomes, including impaired physical and mental health.

We refer to this idea as the *PAR-mismatch hypothesis*. Although scholars who promote adaptive hypotheses in the DOHaD literature view phenotype-environment mismatch as only one of a variety of several reasons why evolved mechanisms of adaptive plasticity may produce maladaptive outcomes (Conradt et al., in press; Hanson & Gluckman, 2014; Kuzawa & Quinn, 2009). ~~But nonetheless~~, it is a reason that is often given considerable explanatory prominence.

The best-known application of the PAR-mismatch hypothesis is the idea that intrauterine starvation prompts the development of altered insulin function and glucose metabolism (Barker, 1994). These changes can lead to diabetes and hypertension, and so are often seen as pathological. However, according to the PAR hypothesis, the negative effects are due not to the early conditions per se, but the mismatch between the early

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~~conditions and the later environment (in which, in affluent societies, resources are usually plentiful). These metabolic processes changes may be adaptive would actually be beneficial~~ if individuals ~~are likely to went on to~~ experience chronic or temporary starvation in adulthood (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004, 2010; Gluckman et al., 2005, 2010). ~~If, however, resources are plentiful in the adult environment (developmental mismatch), the individual is at increased risk for health problems (e.g., diabetes, hypertension)~~—Consistent with this view are studies showing that the harmful effects of early starvation are in some cases attenuated or even absent if, matching early life conditions, the adult environment continues to be lacking in resources (e.g., Stanner et al., 1997; Stanner & Yudkin, 2001).

Another well-known application is the *Stress Inoculation Hypothesis* (Garmezy, 1991), which actually preceded the PAR-mismatch hypothesis in the DOHaD literature. This hypothesis proposes that exposure to mild stressors early in life prepares individuals to cope better with stressors later in life, and so these individuals have better outcomes than unprepared individuals, who are mismatched (Rutter, 1993). Consistent with this hypothesis are studies suggesting that adolescent rats exposed to social defeat are better able to cope with an aggressive male as adults than non-stressed controls (Buwalda et al., 2013; for a review of related results in mice, see Macri et al., 2011). Similarly, squirrel monkeys who experienced brief separations from their mothers as infants were better able to cope with separations later in life than controls (Lyons et al., 2009). And a recent study in humans suggests that immigrant children born to expatriates are less likely to develop affective, personality, and substance use disorders than other immigrant groups (Cantor-Graae & Pedersen, 2013; Nederhof, 2013). A caveat is that studies of stress inoculation

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typically define 'better coping' in terms of health and well-being, rather than fitness, the true currency of natural selection (Belsky, 2008; Ellis et al., 2012; Frankenhuis & Del Giudice, 2012).

Mismatch between early and later environmental conditions has also been implicated in the development of cognitive and socio-emotional abilities in children and adolescents (Frankenhuis & Del Giudice, 2012; Glover, 2011; Glynn & Sandman, 2011; Nederhof & Schmidt, 2012). There are few studies, but initial findings are remarkable. In a recent article titled *“Prescient Human Fetuses Thrive,”* Sandman and colleagues (2012) report that infants who experience congruent levels of maternal depression before and after birth (high or low levels) show superior motor and mental development in their first year, compared with infants who experience incongruent levels of maternal depression (low prenatal and high postnatal levels, or vice versa). These authors argue that already inside the womb, infants start tailoring their brains and bodies to future conditions and benefit if their prenatal and postnatal environment match, even if both are stressful (for related research on non-human animals, see Schmidt, 2011; Homberg, 2012). In short, some findings on metabolism and cognitive and socio-emotional outcomes support what Gluckman and Hanson (2010) have described, perhaps prematurely, as “the emerging consensus”: harmful effects reflect “the maladaptive consequences of developmental plasticity, arising from discordance between the triggering and later environments” (p. 21).

The goal of this paper is to extend and challenge the this emerging consensus based on three insights provided by recent mathematical modelsmodeling. All three of these insights, which show demonstrate the power of *environmental noise* (i.e., imperfect

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indicators of current and future conditions) in shaping development. -The models we discuss explore two sources of environmental noise. First, organisms do not have direct access to the statistics (or *states*) of their environments (e.g., the level of danger). Rather, they may estimate (or ‘infer’; no conscious process implied) these states based on *cues*, i.e., observations that are more likely to occur in certain states of the world than in others. Second, the current state of the world is probabilistically correlated with future states of the world. So, even if our estimate of today is correct and precise, we can only make informed guesses about tomorrow, as in weather forecasting. Evolutionary models of development tend to ignore perceptual noise; they assume that individuals make accurate observations (e.g., detecting an angry face). Instead, they focus on the challenges of using these observations to infer the present state of the environment (e.g., the current level of danger) and predict future environmental states (e.g., future levels of danger).

All these models are by design simplified versions of reality that capture only some essential components of a process or a system (Frankenhuis et al., 2013; Frankenhuis & Tiokhin, 2018; Houston & McNamara, 1999; Levins, 1966; Mangel & Clark, 1988). Each model makes particular assumptions, which may be criticized. The models we discuss, for instance, assume that natural selection has perfectly adapted developmental systems to their environment (this does not imply that every individual is optimally adapted; see below). This *phenotypic gambit* (Grafen, 1984) allows researchers to ignore matters of genetic and physiological instantiation (Maynard Smith et al., 1985). The gambit is a methodological stance that provides a starting point for research. If observations contradict model predictions, we need to refine our model. Statistician George Box (1976) famously remarked that all models are wrong but some

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are useful. Simple models However, models can be extremely useful because they increase precision, make assumptions clear and explicit, remove ambiguities from natural language, ensure logical consistency in argumentation, generate novel predictions, and provide a better understanding of complex interactions that are impossible to intuit without the help of formalizations. The utility of any particular model will depend, of course, on the assumptions it makes and how well it is constructed and analyzed. And, all models are limited. It is key to understand and acknowledge what a model can tell us and what it cannot.

**Modeling development**

All traits of organisms (phenotypes) result from development, i.e., are the product of a process that begins with the zygote and proceeds during the subsequent lifetime.

Hence natural selection can only modify phenotypes by shaping *developmental systems*, i.e., the array of factors (e.g., genes) and processes (e.g., gene regulation) that give rise to phenotypes (Bjorklund et al., 2007; Dall et al., 2015; Frankenhuis et al., 2013; Mangel & Ludwig, 1992; McNamara et al., 2016; West-Eberhard, 2003). Natural selection favors systems that tend to construct *'adaptive'* phenotypes, which increase fitness. The term *'fitness'* is often used to denote individual survival and reproduction. However, fitness should actually be assigned to developmental systems (or strategies, genotypes), not to individuals, and the appropriate measure of fitness depends on the environmental context and species. The distinction between developmental systems and individuals is crucial because, as we will see, optimal systems often produce detrimental outcomes for some individuals (Frankenhuis & Del Giudice, 2012). ~~A given developmental system can produce a variety of phenotypes and natural selection acts on the developmental system~~

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~~through its action on the entire distribution of phenotypes.~~

Individuals change over time, depending on influences internal (e.g., glucose levels) and external to the body envelope (e.g., resources in the environment). Models describe such changes using *state variables*, which quantify the current state of the individual and predict its future state, if only probabilistically. State variables can represent any factor of interest. For example, a model of growth might describe the composition of the body using variables representing skeletal size, bone density, muscle mass, fat levels, the types of tissues present and their degree of differentiation, patterns of gene methylation, brain wiring, hormone levels, receptor densities, etc. Each variable takes on a specific value, which might change over time. Age is typically not a state but rather a crude aggregate measure, because individuals of the same age might be in different developmental and physiological states.

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Developmental models require an *initial state*, which depends on the research question. For models of epigenetics, the initial state could specify which genes are methylated or hormone levels inherited from parents; for models of social learning, an individual's knowledge before any social interactions have occurred. State changes occur throughout the lifetime, but early changes are often the most important as these have lifelong effects. To understand the fitness consequences of early developmental responses, it is necessary to take later effects into account. For instance, chronic activation of stress responses early in life might increase immediate survival (by protecting against threat), but may also accelerate telomere attrition and associated aging, reducing fecundity later in life (Herborn et al., 2014; Metcalfe & Monaghan, 2001).

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Models describe developmental processes by changes in the values of state

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variables. Because development in real organisms is multifactorial (i.e., it depends on the interactions between many different factors and processes), and small differences in these factors and processes can affect outcomes, development is often modeled often as a stochastic process (i.e., the transitions between states are probabilistic, yet certain outcomes might be more likely than others). ~~Even~~ Even if we know an organism's current state, we cannot predict its next state with certainty. Some sources of stochasticity are internal. If an animal ingests food, it burns some fraction, stores another, and excretes the remainder. We can predict patterns (e.g., store more if winter is coming), but not exact amounts, because "cellular metabolism is inherently stochastic, and a generic source of phenotypic heterogeneity" (Kiviet et al., 2014, p. 376). Other sources are external. If an animal forages, it might find food, encounter a mate, contract disease, be predated on, or be killed by a rival. The probabilities of these different outcomes depends on the animal's foraging behavior (e.g., hunting for large rewards in an open field, or for small rewards in a safer refuge), which in turn depends on its state (e.g., hunger level, calories needed to survive the night, migration, or hibernation).

Despite stochastic influences, state changes are not completely at random. The probability that a given change in state will occur (e.g., energy increase) depends on interactions between the environment (e.g., food availability, density of predators) and the developmental system (e.g., behavior, metabolic efficiency).

Animals typically attempt to increase their knowledge about the environment to respond to it appropriately (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). In particular, an animal might use cues, that is, observations that provide *information*

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(reduce uncertainty) about some relevant dimension, to improve its estimate of the current conditions (e.g., dead conspecifics indicate predators). An animal might also estimate future conditions, forecasting ~~hours~~ the future over the timescale of hours (e.g., barometric changes predict thunderstorms), seasons (e.g., a mild winter predicts a mild summer), or even generations (e.g., current abundance predicts adequate nutrition for future offspring) (Botero, Weissing, Wright, & Rubenstein, 2015). Cues are often imperfect: they reduce uncertainty, but do not eliminate it. Moreover, individuals are likely to sample different cues, resulting in estimates that diverge even for individuals in the same environment, which might produce variation in phenotypes (Fischer et al., 2014; Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016). Animals also use social cues (Taborsky, 2017). A potential mate might show courtship cues, which probabilistically predict its willingness to have sex. A rival might show threat signals, which predict its ability to fight. On both immediate and developmental timescales, organisms are continually making consequential decisions under uncertainty in an ever-changing world.

~~— Faced with uncertainty, developmental systems produce individuals that do as well as they can, given the current circumstances, across the range of conditions experienced by ancestors (Dall et al., 2015). Nevertheless, because cues are imperfect, developmental mechanisms do ‘get it wrong’ sometimes (Houston & McNamara, 1999; Mangel & Clark, 1988). An optimal system can get it wrong because, even if it always made the correct decisions (e.g., go forage) given the current information (e.g., cues indicate the weather will likely be stable), the world is to some degree unpredictable (e.g., an unlikely thunderstorm might happen). The system has evolved to produce the~~

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phenotype that is statistically most likely to be appropriate (i.e., to maximize the expected fitness of the developmental system) given the set of inputs; this does not mean it will produce the best actual outcome in every individual case. Moreover, we do not expect systems to be exactly optimal, because although systems have been shaped by past conditions, the range of possible environments is enormous (Dall et al., 2015). So, evolution will not have 'tested' all possible systems in all possible environments, favoring the system that makes the best decisions in all circumstances. Instead, we expect systems that make good decisions on average across environmental conditions (McNamara & Houston, 2009). So, what might a model look like? We may be interested in the question whether it is biologically adaptive to mature earlier in a high-mortality environment (Belsky et al., 1991; Ellis, 2004; Nettle et al., 2013). To study this question, we can build a model examining when it is adaptive for developmental systems to accelerate their rate of maturation based on early life experiences versus mature at a fixed rate (i.e., irrespective of experience)? The answer will depend on the environment. We can, for instance, imagine an environment that fluctuates between different states (e.g., safe or dangerous) during the lifetime of an individual. These states are auto-correlated over time; i.e., this year's level of mortality predicts next year's level, but not perfectly. We may then use an optimization technique to compute optimal developmental strategies, which specify the best decision for every possible state of the developmental system. This analysis might show that if only auto-correlation is very high, early life experience tends to provide an accurate forecast of adult conditions; and hence, individuals should use it. By contrast, if auto-correlation is moderate or low, early life experience provides a poor forecast of adult conditions and might actually be

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misleading. In that case, developmental systems might do better by maturing at a fixed rate that is adapted to the average level of mortality over evolutionary time (Nettle et al., 2013). This result is theoretically interesting because it contradicts the intuition that as long as there is *some* auto-correlation in the environment, it is adaptive to tailor developmental trajectories based on early life experience. Empirically, it highlights the importance of actually measuring the statistics of environments (which is rarely done in current research) in order to assess the plausibility of evolutionary explanations, such as the PAR-mismatch hypothesis.

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**Detrimental outcomes in a stable environment**

The PAR-mismatch hypothesis regards developmental mismatch as a key source of departure from optimal health and wellbeing. Such mismatches result from changing conditions over the course of ontogeny (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2004, 2010; Gluckman et al., 2005, 2010). The PAR hypothesis guides much empirical research on early life effects, and has been incorporated into several influential theoretical frameworks in psychology. (Please note that, such as Differential Susceptibility Theory (Ellis et al., 2011), which concerns individual differences in levels of plasticity, and the Adaptive Calibration Model (Del Giudice et al., 2011), which addresses individual differences in stress response systems. We use the term ‘early life effects,’ rather than ‘developmental programming,’ in order to avoid a deterministic connotation of deterministic development. Early-life experience can may have a lasting impact on affect adult traits, even if these traits but these traits may continue to exhibit a some degree of substantial degree of plasticity; (Takesian & Hensch, 2013).)

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To illustrate, the theory of Biological Sensitivity to Context (Boyce et al., 1995; Boyce & Ellis, 2005) proposes that individuals evolved to tailor their levels of plasticity to expected future conditions, with the potential for developmental mismatch being a cost of increasing levels of plasticity (Del Giudice & Ellis, 2016; Ellis et al., 2011). The Bet-hedging Hypothesis of Differential Susceptibility (Belsky, 1997) states that it is adaptive for parents to produce offspring with varying levels of plasticity, based on the idea that plastic offspring thrive when current cues correctly prepare them for future conditions, but suffer when current cues provide an unreliable forecast (e.g., when a child socially learns outdated knowledge and behavior from its caregivers), resulting in developmental mismatch; hence, the argument goes, parents produce less plastic offspring as well, which are less affected by current cues (Belsky, 2005; Belsky & Pluess, 2009; Ellis et al., 2011; for a model, see Frankenhuys et al., 2016). The Adaptive Calibration Model (Del Giudice et al., 2011) posits that early life experience *calibrates* the stress response system and life history strategies (e.g., the timing of puberty) to the challenges an individual is likely to encounter during its lifetime, which is thought to be adaptive on average, but may result in health costs if later conditions differ substantially from earlier conditions (e.g., when a child develops in a dangerous and unpredictable neighborhood or family and then moves into a safe and supportive school, yet continues to use coercive behavioral strategies that worked well in its initial environment to accomplish goals, which might result in peer rejection, which in turn could produce physical and mental health problems).

We agree that developmental mismatch can result from changing conditions over ontogeny. However, even evolutionary developmental psychologists it is sometimes often overlooked that inferring the present state of the world poses challenges for

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organisms, just as predicting future conditions does. ~~T (i.e., the present conditions do not automatically 'get under the skin' or become 'biologically embedded' with perfect accuracy).~~ *-State-dependent optimality modeling is a suitable method that is used in biology to determine adaptive decisions in a particular environment, when decisions are interdependent over time, meaning that past decisions affect future options (Houston & McNamara, 1999; Mangel & Clark, 1988; for explanation tailored to psychologists, see Frankenhuys et al., 2013, 2018).* Such modeling clearly ~~Mathematical models~~ shows that even ~~when if the an~~ environment is *completely* stable within lifetimes, noisy environmental cues often produce substantial mismatch between *some individuals'* ~~phenotypes~~ *the conditions for which the organism is adapted,* and ~~the~~ actual conditions ~~that obtain~~ (Frankenhuys & Panchanathan, 2011; Panchanathan & Frankenhuys, 2016; Meacham & Bergstrom, 2016). Such mismatch even occurs when individuals: (a) have the opportunity to *repeatedly* sample cues ~~repeatedly~~, (b) obtain cues at no cost throughout their entire lifetimes, and (c) there is a cost to being mismatched. -These mismatches do not result from malfunction; rather, they are produced by a developmental system responding optimally to noisy inputs in a context it is evolutionarily adapted to.

To illustrate, an optimal decision rule can produce *excessive anxiety in some individuals* ~~maladaptive anxiety~~ in a stable, safe environment (Meacham & Bergstrom, 2016). Consider agents that have opportunities that are either profitable or dangerous. Before pursuing or declining an opportunity, an agent samples a cue informative about the level of environmental danger. Next, an agent chooses to pursue or decline, following the optimal decision rule (which maximizes its expected fitness). If an agent pursues, there is a good or bad outcome, and an agent gains additional information about

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the level of danger. If an agent declines, however, it does not gain further information (e.g., a rabbit leaving its burrow in order to forage learns more about the environment than one that remains in its burrow). Because cues are stochastic, some individuals sample more danger cues than others before making decisions. These individuals may set their sensitivity to threat higher than necessary, becoming overly anxious. Their anxiety, in turn, leads them to decline opportunities, preventing them from learning the environment is actually safe. Accordingly, the model “predicts that disorders of excess anxiety will be common but disorders of insufficient anxiety will be rare” (Bergstrom & Meacham, 2016, p. 216; for related signal detection models exploring the evolutionary origins of mood disorders, see Bateson et al., 2011; Nettle & Bateson, 2012; for a model showing that depression can result from following an optimal decision rule in a changing environment, see Trimmer et al., 2015).

Mathematical models generally show that developmental mismatch is more likely to occur when systems have been exposed to greater environmental variability over evolutionary time (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). A system that has evolved in a variable environment is uncertain about the conditions early in ontogeny. Models represent the distribution of environmental states experienced by a species as a prior probability distribution (*a priori*). If a species experienced a narrow range of environmental states, the prior is centered on those states, and the system starts out with a good estimate, if the current environment is still within the range the system has evolved in. By contrast, if a species experienced a wider range, the prior is more dispersed, and so it will be more challenging for the developmental system to match phenotypes to

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current conditions. Note, however, that if an environmental state is truly novel, meaning it has never occurred before in a species' evolutionary history, developing individuals should assign zero probability to it, irrespective of the shape of their priors. Hence, it is challenging if not impossible to model responses to completely novel environments within a Bayesian framework ([for discussion of the applications and limitations of the Bayesian optimality models, see Bowers & Davis, 2012; Gopnik & Bonawitz, 2015; Griffiths et al., 2010; Mangel, 1990; Ramírez & Marshall, 2017; Trimmer et al., 2012](#)).

Mismatch is also likely when systems only have access to low-reliability cues, as these cues help little in discriminating between different environmental states (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). When cue reliability is very low, organisms might ignore cues altogether, and evolve non-plastic strategies, such as diversified bet-hedging, producing fixed offspring of different types, guaranteeing that some fraction of them will match the current environmental state (Donaldson-Matasci, Lachmann, & Bergstrom, 2008; Frankenhuis et al., 2016; Leimar, Hammerstein, & Van Dooren, 2006; McNamara et al., 2016; Seger & Brockmann, 1987). Such bet-hedging illustrates a point we made earlier: fitness should be assigned to strategies, not to individuals. Natural selection might result in strategies that produce detrimental outcomes for some individuals.

Even systems that do have access to moderate-reliability cues, however, might produce some individuals that are substantially mismatched. Such mismatch is likely to occur when it is adaptive to commit to a developmental trajectory early in life, even if doing so implies having had few opportunities to learn about the environmental state, thus increasing the risk of mismatch. Committing early might be favored, for example,

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when it takes time to build conditional adaptations (e.g., predator defenses) that yield high fitness in specialized form, if they are well matched (Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016). A general lesson is that natural selection maximizes the fitness of developmental systems (not of individuals), and these systems are likely to produce some mismatched individuals, even when [these systems](#) functioning optimally in a context they are evolutionarily adapted to.

### Variation in plasticity between and within individuals

[Why do some adopted children adapt swiftly to their new environment, while others remain burdened by their difficult past? And, why do different mental systems within these children adapt at different rates to new conditions \(Zeanah et al., 2011\)?](#)

Biologists have wondered why all organisms are not Darwinian demons, i.e., why they are unable to always perfectly match their brains, bodies, and behavior to the current conditions. Of course, organisms do retain some degree of plasticity in many traits and behaviors throughout their lifetimes. This degree of plasticity, however, tends to change (increase or decrease) over the life course, and individuals differ in their trajectories of change. The term ‘sensitive periods’ describes periods or states in which experience shapes a given trait or behavior to a larger extent than other periods or states (Fawcett & Frankenhuis, 2015). Importantly, sensitive periods do not imply ‘critical periods’, in which the impact of experience is limited only to a particular period or state, with irreversible effects (Takesian & Hensch, 2013). Recent mathematical modeling shows that optimal developmental systems may produce species-typical sensitive periods in development as well as individual differences in sensitive periods, even in environments that are stable within lifetimes ([Fawcett & Frankenhuis, 2015](#); [Frankenhuis & Fraley,](#)

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[2017](#). There are several reasons for ~~the latter~~[this variation](#).

Individuals might start out with different priors because they have inherited different information from their distant ancestors (e.g., via genes) or from their immediate ancestors (e.g., via parental effects or inherited epigenetic factors) (Dall et al., 2015; Jablonka, Oborny, Molnár, Kisdi, Hofbauer et al., 1995; Hanson & Gluckman, 2014; [Kuzawa, 2005](#); Lachmann & Jablonka, 1996; Marshall & Uller, 2007; McNamara et al., 2006; Stamps & Krishnan, 2014; Stamps & Frankenhuis, 2016; Trimmer et al., 2011; Uller, 2008; Uller, English, & Pen, 2015). Priors can differ in their means and variances. Individuals whose ancestors have been exposed to higher levels of harshness (e.g., war, famine) might take longer to adjust to beneficial conditions, as their personal experience is more discrepant with inherited information. Individuals whose ancestors have been exposed to greater environmental variability might adjust more flexibly when their experience is discrepant with inherited information, because their priors are more dispersed. The extent to which experience (e.g., adversity) affects individuals at some life stage thus depends partly on their inherited priors.

Individuals might sample cues of different reliabilities. The reliability of a cue depends on its likelihood of occurring in different states of the environment. A cue is more reliable to the extent that it is differentially likely to occur in different states of the world, thus allowing for discrimination between these states (Dall et al., 2015; McNamara et al., 2006; Moran, 1992; Sultan & Spencer, 2002; Trimmer et al., 2011; Stamps & Frankenhuis, 2016). For example, a child who observes that her entire community suffers from death and disability can draw a stronger inference about environmental conditions (i.e., conditions are harsh) than a child who occasionally

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observes a little suffering in some adults. The reason is that widespread and severe suffering is unlikely to happen except when conditions are harsh, whereas some occasional suffering could happen even in beneficial conditions, if there is a streak of bad luck due to chance (e.g., minor injuries happening to different people in the same village). Children experiencing more reliable cues might reduce their uncertainty about environmental conditions faster, reducing their plasticity earlier in life than children experiencing less reliable cues (Frankenhuis & Panchanathan, 2011; Panchanathan & Frankenhuis, 2016). The ‘reliability’ of cues (the extent to which the frequency of a cue varies between different states of the environment) should be distinguished from their ‘information value’ (the extent to which they reduce uncertainty; this depends both on the cue reliability and on current knowledge) and their ‘fitness value’ (the extent to which optimal use of the cue increases fitness; Donaldson-Matasci, Bergstrom, & Lachmann, 2010; McNamara & Dall, 2010; Pike, McNamara, & Houston, 2016). Moreover, the extent to which organisms can discriminate between different environmental states depends both on the cue reliability and on the ability of sensory systems to accurately perceive cues. Discrimination is a product of cue reliability discounted by perceptual inaccuracy.

Even when classes of cues are reliable and well perceived, individuals might receive misleading instances of those cues, by chance variation akin to sampling variation in classical statistics. This will result in estimates that diverge between individuals in the same environment. ~~Even when cues are equally reliable and equally well perceived, individuals might sample different cues, resulting in estimates that diverge,~~ which affect

the retention and decline of plasticity (Frankenhuis & Panchanathan, 2011; Panchanathan

**Comment [DN1]:** In this sentence, the first use of ‘cue’ is the cue-type (which has a defined reliability), and the second use of ‘cue’ is the cue-token (for which reliability is not defined, since there is only one cue and one outcome, and you can’t calculate a correlation for a single event). For example, clouds might be a reliable cue of rain on average, but the individual token of the cloud I see today might prove misleading. How about:

“Even when classes of cues are reliable and well perceived, individuals might receive misleading instances of those cues, by chance variation akin to sampling variation in classical statistics. This will result in estimates that diverge between individuals in the same environment....”

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& Frankenhuis, 2016). As cues are noisy, some individuals will have more consistent experiences than others (e.g., all safe cues vs. some safe and some danger cues).

Mathematical models show that individuals who have more consistent experiences reduce their uncertainty at faster rates, hence may lose their plasticity earlier in their lives, even to the point of irreversibility—i.e., critical periods (Fawcett & Frankenhuis, 2015; Frankenhuis & Fraley, 2017). For example, when two people live in an affluent neighborhood in which robberies rarely occur, one might be victimized twice, the other never. As both have beneficial experiences as well, the victim overall has more heterogeneous experiences (some good and some bad ones). Hence, this individual might retain more plasticity for longer, adjusting more easily to harsher conditions if their environment changes.

In addition to the variation in priors, cue reliabilities, and stochasticity in cues, mathematical models also suggest other factors that should affect the retention and decline of plasticity over the life course. These factors include developmental variation in: (a) the availability of cues, (b) the fitness benefits of information, and (c) the fitness costs of plasticity (Fawcett & Frankenhuis, 2015). The crucial point for now is that inferring the present state of the world poses challenges for organisms, just as predicting future conditions does, and responses to these challenges may help to explain individual differences in early life effects observed in empirical studies.

### **Predicting future somatic states**

A researcher who documents an early life effect might be tempted to infer that the effect evolved in an environment that was stable within individual lifetimes; why else would the organism rely on early experience in setting adult phenotype? This inference,

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however, is not necessarily warranted. Mathematical models show that there are at least two distinct, but mutually compatible, adaptive reasons for the evolution of early life effects: external and internal Predictive Adaptive Responses (PARs; Nettle et al., 2013; Rickard et al., 2014; Wells, 2012, p. 262, suggests a similar distinction).

The external PAR account proposes that some early life effects *have evolved in response* to factors in the external environment (e.g., intrauterine under-nutrition) that forecasted future environmental conditions (e.g., famine in adulthood) (Bateson, 2001; Bateson et al., 2004; Gluckman & Hanson, 2010). On this view: “the organism presets its physiology in expectation of that physiology matching its future environment. PARs, therefore, are a form of phenotypic plasticity in which the resulting phenotype is not necessarily advantageous in the environment concurrent with or immediately following the inducing cue, but is likely to be advantageous in an anticipated future environment. The cue thus acts as a predictor of the nature of this environment” (Gluckman et al., 2005, p. 527).

The internal PAR account, in contrast, proposes that early life effects *have evolved because* early experience alters future life prospects by having irreversible effects on future bodily states (e.g., through limiting growth, increasing oxidative stress, or accelerating telomere attrition) (Figure 1). Such limitation brings about a correlation between early experience and adult prospects, irrespective of future environmental conditions (Nettle et al., 2013; Rickard et al., 2014). Internal PARs are more than developmental constraints (Lea, Altmann, Alberts, & Tung, 2015); they are adaptive responses to such constraints that tailor individuals to their predicted somatic futures. Crucially, the internal-external PAR distinction exists at an ultimate level of explanation

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(evolutionary history and adaptive value), and not at a proximate level (developmental and physiological processes). At a proximate level, all PARs are mediated by somatic processes, and these processes may or may not be similar for different PARs (for discussion of differential predictions at a proximate level, see Rickard et al., 2014).

[ INSERT FIGURE 1 ABOUT HERE ]

Mathematical models show that external and internal PARs can both evolve, but do so in different conditions (Nettle et al., 2013; Del Giudice, 2014). Natural selection favors external PARs only when environmental conditions are stable over individuals' lifetimes (e.g., if the world is harsh today, it will likely be harsh next year). Internal PARs do not require such stability; rather, these require that individuals' somatic conditions are stable over their lifetimes (e.g., if my body was fragile this year, it will likely be fragile next year) (Figure 1). If an environment is completely unpredictable, natural selection does not favor external PARs, but it is likely to favor internal PARs, if earlier somatic states are correlated with later ones. Such somatic autocorrelation exists in many species (~~see Berghänel et al., 2016; Blackburn et al., 2015; Douhard et al., 2016, for references~~). - For instance, telomeres, the protective 'caps' on the end of chromosomes, are considered markers of life's insults (Blackburn et al. 2015), in that they are affected by a variety of exposures to stress and adversity. Telomeres shortened in early life tend to remain short for the rest of life, and telomere length appears to be a good predictor of future health and longevity in humans (Bakaysa et al., 2007; Kimura et al., 2008; Njajou et al., 2009). The most compelling cases for external PARs have been

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documented in organisms that are short-lived and/or sessile, in which there is not much scope for the environment to change in between the receipt of early cues and the environment of selection, such as certain species of fungi (Markiewicz-Potoczny & Lydall, 2016), plants (Galloway & Etterson, 2007), and crickets (Storm & Lima, 2010).

Studies in humans, however, suggest that having a good start in life (a silver spoon) improves fitness more than matching environmental conditions early and later in life (e.g., Hayward & Lummaa, 2013; Hayward et al., 2013; Wells, 2007; Wells & Johnstone, 2017). Perhaps this is because humans are long-lived, like the macaques and reindeer, to which we turn next.

Recent studies suggest the existence of internal PARs in wild long-lived animals, ~~such as reindeer and macaques,~~ that inhabit ecologies that might be too unpredictable for external PARs to evolve. For instance, Assamese macaque (*Macaca assamensis*) that inhabit Southeast Asian forests experience highly unpredictable environmental conditions: the year-to-year predictability of food abundance and rainfall is very low, so that it is not possible to use early life cues to predict later environmental conditions. Nonetheless, in this species, offspring whose energy intake is reduced early in life as a result of their mother's physiological stress display accelerated growth, consistent with their pursuing a fast life-history strategy (see Berghänel et al., 2016;-). Similarly, living at high latitudes, Svalbard reindeer (*Rangifer tarandus platyrhynchus*) experience major variation in resources in the winter due to variation in rain-on-snow events, which create ice layers on the ground or in the snow that limit access to vegetation. Female reindeer that experienced many rain-on-snow events in utero tend to be relatively light and small during both the juvenile and adult stages. Despite this somatic disadvantage, these

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[females attain reproductive success in the first six years of their lives comparable to females of higher somatic quality, who had better access to vegetation early in ontogeny. Their rough start in early life manifested only among females aged 7 years and older, who had lower annual reproductive success. The females of lower-somatic quality engaged in reproductive events at a lower body mass than females of higher-somatic quality. This increased investment in reproduction probably evolved not as a response to predicted future environmental conditions, but rather as a response anticipating accelerated somatic decline](#) (Douhard et al., 2016).

\_\_\_\_\_ Studies of human development show correlations between early somatic state and later phenotypic outcomes, even if early somatic state is not correlated with early environmental stress, or after controlling for such stress. For example, British girls who experienced chronic disease in childhood develop earlier timing of first reproduction, even if chronic disease is not correlated with environmental stress, such as father absence and socioeconomic status (Waynforth, 2012; see also Hill et al., 2016; Valencia & Cromer, 2000). Similarly, Danish data show that low birth weight in girls and boys predicts lower levels of trust in adulthood, even after controlling for childhood family environment. Low birth weight predicts small body size and physical vulnerability later in life, which might increase the risk of being socially exploited, making vigilance adaptive (Petersen & Aarøe, 2015). A longitudinal study in the US supports both the internal and external PAR hypotheses. It shows that even after controlling for internal health, early-life adversity predicts greater adolescent risk-taking, problematic functioning, and earlier age of menarche (for girls); and, internal health mediated the relation between the early environment and adolescent behavior (Hartman et al., [in](#)

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[press2017](#); see also Chua et al., 2017). This finding highlights the fact that the internal and external PAR accounts are mutually compatible: individuals might tailor their development to ~~both~~ predicted future environmental [states and as well as](#) future somatic states.

**Implications for DoHaD**

We have argued that environmental noise has the potential to: (a) produce detrimental outcomes for some individuals, even for an optimally functioning system in a stable environment, (b) cause individual differences in the timing and reversibility of sensitive periods, and (c) favor early life effects tailored to predicted future somatic states, instead of or as well as predicted future environmental states. We conclude with a brief discussion of the implications for DoHaD.

The first implication is that is important to explicitly incorporate noise in theory development. That is, models of the evolution of developmental systems cannot simply assume that individuals know environmental conditions perfectly, or that every individual experiences the average environment. Rather, techniques such as stochastic dynamic programming are required ([Frankenhuis et al., 2018](#); Houston & McNamara, 1999; Mangel & Clark, 1988), which explicitly incorporate the fact that average properties of environments lead to probability distributions of experience, with different individuals receiving different sequences of experience as a matter of course.

Second, a ~~very~~-general implication of the material reviewed is that the normal outcome of evolved developmental systems is a great degree of variation, both in final phenotype, and in the timing of the phenotype's development ([Holmes & Patrick, 2018](#)). Extensive variation emerges even if the developmental system is operating normally; i.e.,

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if there is no 'pathology' in the strict sense (Cosmides & Tooby, 1999; Wakefield, 1992, 1999; [for recent discussion, see Griffiths & Matthewson, 2016; Matthewson & Griffiths, 2017](#)). DoHaD has also tended to focus particularly on mismatch between early developmental and adult conditions as a source of deleterious phenotypes. However, as we have argued, a certain fraction of the population should be expected to show deleterious phenotypes even when there is no such mismatch. Essentially, noise requires us to shift focus from the expectation that *individuals* will be optimally adapted to their environment (if there is no pathology or environmental change). Instead, developmental *systems* are the outcome of adaptive evolution, and systems, through their interactions with noisy environments, produce clouds of phenotypic variation at the individual level (Barrett, 2015). Many of those individuals survive and reproduce successfully (otherwise the system could not persist), but not all will do so.

Thus, when explaining disease states from an evolutionary perspective, we cannot, without further evidence, make strong inferences that the cause is mismatch between developmental and adult environments. More positively, techniques such as stochastic dynamic programming allow us to build sophisticated models of developmental systems from which the consequences of different kinds of environmental change and developmental input can be simulated. These predictions are at the level of phenotypic distributions, not individual phenotypes, and so they have considerable empirical relevance to the changing population burden of health and disease. For example, dynamic models predict that the distribution of body fat stores will be affected by (imperfect) cues of food scarcity, and will under many conditions contain more individuals with excess fat than with insufficient fat, because of the historical strength of

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selection on avoiding starvation (Higginson, McNamara, & Houston 2016; Higginson & McNamara 2016). This prediction may help explain why the prevalence of obesity can be, apparently paradoxically, increased rather than decreased by food insecurity and restrictive dieting (see also Nettle, Andrews, & Bateson 2017).

A third implication is that longitudinal studies are important (Clutton-Brock & Sheldon, 2010), because early experience should strongly affect later development, in complex and path-dependent ways. This premise has always been a strength of DoHaD. We note in particular the potential relevance of longitudinal studies of wild-type animals under ecologically realistic conditions. Using inbred model strains under standardized developmental conditions is generally favoured in biomedical science, for reasons of experimental control, but it may lead to quite unrealistic expectations about the degree of phenotypic variability that is the normal outcome of development. Having said this, even with inbred strains and standardized conditions, a great degree of phenotypic variability is in fact observed (Freund et al., 2013; Lynch & Kemp, 2014).

Finally, although adaptive hypotheses about early life effects focus on explaining general phenotypic tendencies that emerge in the normal range of environments, formal modeling of these hypotheses does invite further reflection on the distinction between statistical rarity and pathology. Given that the distribution of environmental experiences is probabilistic, and phenotypic development is affected by noise, then extreme phenotypic states will occur with a low frequency in all populations of normally functioning animals. Thus, discovering a state of an organ or system that is rare does not necessarily mean that the system is pathological, in the sense of lesioned or subject to a large deleterious genetic mutation. Rather, the individual may just have had an unlikely

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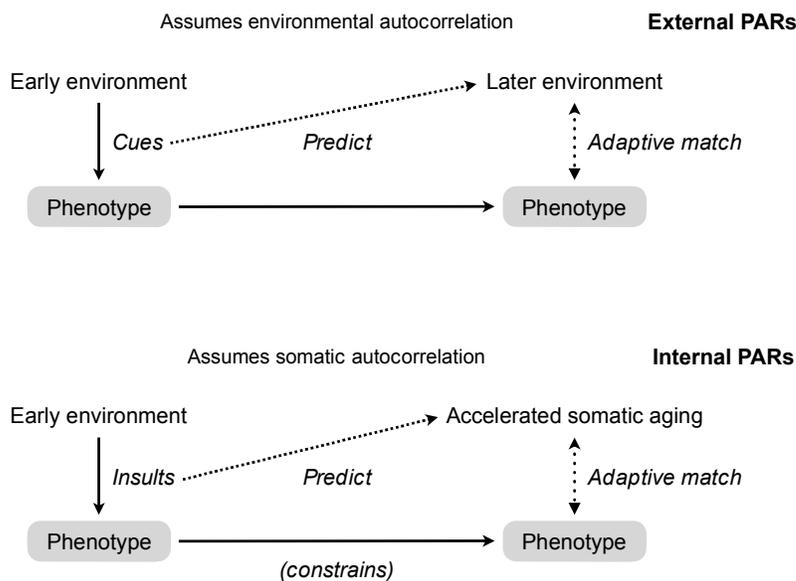
sequence of developmental inputs. They ~~are~~ may be at the edge of the normal cloud.

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**Figure 1 and caption**

The distinction between internal and external PARs: two distinct, but mutually compatible, adaptive reasons for the evolution of early life effects. Whereas external PARs require environmental autocorrelation, internal PARs depend on somatic autocorrelation. Internal PARs can evolve even when environmental autocorrelation is low; external PARs cannot, because it is impossible to forecast future environmental states and adapt to them (Nettle et al., 2013; Rickard et al., 2014). Note: internal PARs are more than developmental constraints; they are adaptive responses to such constraints that tailor individuals to their predicted somatic futures.



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