Epigenetics and the maintenance of developmental plasticity: extending the signalling theory framework

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/brv.12396

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ABSTRACT

Developmental plasticity, a phenomenon of importance in both evolutionary biology and human studies of the developmental origins of health and disease (DOHaD), enables organisms to respond to their environment based on previous experience without changes to the underlying nucleotide sequence. Although such phenotypic responses should theoretically improve an organism's fitness and performance in its future environment, this is not always the case. Herein, we first discuss epigenetics as an adaptive mechanism of developmental plasticity and use signaling theory to provide an evolutionary context for DOHaD phenomena within a generation. Next, we utilize signalling theory to identify determinants of adaptive developmental plasticity, detect sources of random variability – also known as process errors that affect maintenance of an epigenetic signal (DNA methylation) over time, and discuss implications of these errors for an organism's health and fitness. Finally, we apply life-course epidemiology conceptual models to inform study design and analytical strategies that are capable of parsing out the potential effects of process errors in the relationships among an organism's early environment, DNA methylation,

and phenotype in a future environment. Ultimately, we hope to foster cross-talk and interdisciplinary collaboration between evolutionary biology and DOHaD epidemiology, which have historically remained separate despite a shared interest in developmental plasticity.

Key words: developmental plasticity, signalling theory, epigenetics, DNA methylation, developmental origins of health and disease (DOHaD), predictive adaptive response (PAR), thrifty phenotype.

CONTENTS

I. INTRODUCTION

An individual's genotype is established at conception. Nevertheless, diverse phenotypes may arise from a single genotype in response to an organism's environment. This phenomenon, broadly referred to as 'phenotypic plasticity' (West-Eberhard, 1989), can occur in response to previous environmental exposures, known as 'developmental plasticity', or to concurrent exposures, known as 'contextual plasticity' (Stamps, 2016). Herein, we focus on developmental

plasticity, both as an adaptive response (e.g. modified behaviour, physiology, or structure) that improves an organism's fitness in its projected future environment, and as a non-adaptive consequence of environmental instability and perturbed developmental processes that lead to a mismatch between an organism's phenotype and future environment (Stearns, 1989; West-Eberhard, 1989; Bateson *et al.*, 2004; Bateson, Gluckman & Hanson, 2014; Ghalambor *et al.*, 2007; Nettle & Bateson, 2015). Using signal system and life-course epidemiology frameworks, we explore the temporal relationships among key components of developmental plasticity – namely, the environment experienced by an organism during early life, epigenetics as a mediating biological mechanism, and the organism's phenotype in the future environment. In addition, we consider the role of stochasticity in endogenous plasticity, which is phenotypic variation due to the organism's changing internal state as it ages (Pigliucci, 1998; Stamps, 2016), as a potential source of error in epigenetic processes that underlie developmental plasticity.

Our objectives are threefold. First, we provide a brief summary of the relevant empirical evidence for epigenetic mediation of developmental plasticity in evolutionary developmental biology and in human studies of developmental origins of health and disease (DOHaD). Second, we use a signalling theory framework to illustrate how one specific epigenetic mechanism, DNA methylation, facilitates developmental plasticity. The bulk of this objective focuses on aligning epigenetic mechanisms (proximate explanations) of developmental plasticity with health- and fitness-related outcomes (ultimate explanations) in order to provide an evolutionary context for DOHaD phenomena. Finally, we explore the role of process error in epigenetic maintenance of

developmental plasticity in both evolutionary developmental biology and human health using concepts from signalling theory and life-course epidemiology framework.

II. EMPIRICAL EVIDENCE OF EPIGENETIC SIGNALLING

Epigenetic mechanisms, such as DNA methylation, are relatively stable, mitotically heritable changes in chromosomes that influence the phenotype of an organism within a generation, but are not due to alterations in the DNA nucleotide sequence (Allis, Jenuwein, & Reinberg, 2007; Berger *et al.*, 2009). Our focus is on DOHaD over the life course within a generation, rather than on meiotically stable maternal effects across generations (see McNamara *et al.*, 2016 and references therein). Of particular relevance to this review is the fact that epigenetic changes to the DNA may facilitate developmental plasticity by encoding information from an organism's early life, including the prenatal environment, to coordinate future gene activity and phenotypes in later-life environments (Jaenisch & Bird, 2003; Bird, 2007; Feinberg, 2007). Conceptualizing this process within a signalling framework has direct application not only to the study of human disease, but also to the understanding of evolutionary developmental processes that directly impact phenotypes upon which selection acts (Gilbert & Epel, 2015). We present brief examples of both below.

(1) Insect polyphenisms in evolutionary developmental biology

Insects exhibit extraordinary intraspecific diversity in appearance and behaviour (Applebaum & Heifetz, 1999; Miura, 2005), much of which is induced by environmental stimuli. One of the most conspicuous examples of developmental plasticity is the density-dependent polyphenism of swarming locusts. Both the desert locust (*Schistocerca gregaria*) and the migratory locust (*Locusta migratoria*) have two distinct adult forms: one that is gregarious in behaviour and colourful in appearance, and another that is solitary with drab colouring. These phenotypes stem from a density-dependent cue: physical contact in crowded environments early in life. Specifically, tactile stimulation on the legs of the locust nymph triggers development of the gregarious adult form (Simpson *et al.*, 2001). Although there is an extensive literature documenting the behavioural triggers, ecological factors, and pheromonal mechanisms that influence locust polyphenisms and the extent to which this developmental plasticity is adaptive (Pener, 1991; Pener & Yerushalmi, 1998), the molecular mechanisms have more recently gained prominent interest (Pener & Simpson, 2009; Simpson, Sword & Lo, 2011).

Researchers have identified gene sequences in *L. migratoria* that encode DNA methyltransferases (DNMT), a family of enzymes that catalyse the DNA methylation reaction (Robinson *et al.*, 2011). These DNMTs are differentially expressed between the solitary and gregarious phases in both *L. migratoria* (Robinson *et al.*, 2016) and *S. gregaria* (Boerjan *et al.*, 2011), suggesting that differences in early environment lead to differences in the methylation control machinery. Such differences in DNMT expression can lead to changes in the epigenome, which in turn can alter gene expression and regulate developmental plasticity. Indeed, desert and

migratory locusts have relatively high levels of DNA methylation compared to many other invertebrates (Falckenhayn *et al.*, 2013), and differential methylation has been identified in over 90 genes and non-coding transposable elements associated with adult phenotypes that reflect early-life crowding conditions (Wang *et al.*, 2014; Robinson *et al.*, 2016). The dramatic differences in behaviour and morphology of locusts due to crowding conditions, despite the identical nucleotide sequence in their DNA, provides a compelling example of how epigenetic signals encoded early in life may alter adult phenotypes. Furthermore, because the locust polyphenisms are stable and involve modifications in DNA methylation, this system demonstrates how an epigenetic molecular link can transmit messages over the course of development to induce phenotypic differences later in life; an information-transmission process with parallels to communication in a potentially noisy signal system.

(2) Poor nutrition, thrifty metabolism, and human health

In studies of human health, the field of DOHaD documents plasticity in metabolic phenotype in response to early-life nutrition (Gillman, 2005, 2010; Gluckman & Hanson, 2006; Godfrey, Gluckman & Hanson, 2010). A central hypothesis of DOHaD is that environmental exposures during sensitive periods of development (e.g. the *in utero* period, early infancy, and the pubertal transition) have a greater impact on adult phenotype than those occurring at other times (Gluckman *et al.*, 2005*a*; Barouki *et al.*, 2012). This hypothesis originated from David Barker's observations of higher ischaemic heart disease mortality among persons who were small as

infants – presumably due to poor intrauterine nutrition (Barker *et al.*, 1989). Subsequently, analyses of data from the Dutch Winter Famine of 1944 revealed associations between periconceptional exposure to famine and poor metabolic health in adulthood in a trimester-specific manner (Ravelli *et al.*, 1998; Roseboom *et al.*, 2001; Painter, Roseboom & Bleker, 2005).

More recent work with the Dutch Winter Famine cohort identified DNA methylation as a mechanism linking prenatal famine exposure to poor metabolic health. Heijmans *et al.* (2008) found that adults exposed to famine around the time of conception had lower methylation of insulin-like growth factor 2 (*IGF2*), a maternally imprinted gene that regulates intrauterine growth (Barlow & Bartolomei, 2007), as compared to same-sex siblings not exposed to famine. In a follow up study, Tobi *et al*. (2009) identified six additional loci involved in regulation of growth and metabolism that were differentially methylated in adults prenatally exposed to famine and their non-exposed siblings. These results provide stronger evidence that early nutrition influences DNA methylation, but because genes may be either hyper- or hypomethylated; the potential adaptive function of these alterations as an epigenetic signal warrants additional investigation (Tobi *et al.*, 2009).

Collectively, these examples from insect and human literatures highlight three important facets of developmental plasticity: (1) environmental exposures may affect phenotypes, possibly *via* epigenetic mechanisms, after a long delay, (2) the same environmental stimuli may have different effects on phenotype depending on the timing of the exposure, and (3) environmental

stability affects the likelihood of a mismatch between an organism's phenotype in the predicted *versus* actual environment – a central concept to DOHaD (Godfrey *et al.*, 2007) and a determinant of Darwinian fitness (Gluckman, Hanson & Beedle, 2007; Frankenhuis & Del Giudice, 2012). We suggest below that use of a signalling theory framework illustrates how one specific epigenetic mechanism, DNA methylation, facilitates developmental plasticity.

III. SIGNAL SYSTEMS AND SIGNALLING THEORY

Here, we describe key aspects of a signal system, which includes the signal itself, reliability of signal transmission, and the receiver response, and relate them to epigenetic signalling. Ultimately, we lay the groundwork for Section IV, which relates signalling theory to conceptual frameworks within evolutionary developmental biology and DOHaD.

Signal systems are a key aspect of information theory, which focuses on quantification of information; by contrast, signalling theory is a sub-discipline of evolutionary biology concerned with the adaptive value of a signal, and signal detection theory is a statistical application that deals with prediction based on posterior distributions (Getty, 2014). Despite the subtle differences among the foci of these bodies of theory, they share interest in elucidating how signal systems are influenced by internal and external factors, and assessing the consequences of errors in signal systems. Note that throughout this paper we discuss random variability as types of process errors and signal system noise, both of which are terms that describe the role of

stochasticity in signalling and biological systems. Here, we integrate concepts from each of these fields to discuss signal systems as they apply to an epigenetic signal system.

(1) Signals and information

(*a*) *What is a signal?*

A signal is a structure, an energetic state, or an action that transmits information in order to reduce the receiver's uncertainty about some state of nature (Hartley, 1928; Shannon, 1948, 1949; Maynard Smith & Harper, 2003; Schneider, 2014). Evolutionary biologists distinguish between signals, which evolved because they change the behaviour of receivers in ways that benefit the signaller, and cues, which benefit only the receiver (Maynard Smith & Harper, 2003; Bradbury & Vehrencamp, 2011). In our conceptualization of epigenetically mediated developmental plasticity, the signal of food scarcity, representing the organism's experience of a depauperate environment, would be considered a cue. The epigenetic signal from early to later life of an individual is a true signal if the developmental response is adaptive later in life. As with hormonal signals, the epigenetic signal benefits the sender because of the response of the receiver, which happens to be the same individual. Having noted this distinction between signals and cues, we will adopt the terminology of physical sciences and engineering and, henceforth, refer to both as signals in this review.

Information theory approaches to signalling focus on the information content of signals, measured as uncertainty reduction (Hartley, 1928; Shannon, 1948, 1949; Adami, 2004;

Schneider, 2014). Evolutionary biological approaches to signalling focus on the value of information, measured by how much it can improve fitness (Dall *et al.*, 2005; Getty, 2014; Pike, McNamara & Houston, 2016). Getty (2014) illustrates with the following simple example. In a penny-matching game, the uncertainty in the outcome of a flipped penny is one bit. The value of knowing the outcome and improving the probability of winning the penny from ½ to 1 is half a penny. In the classic story *The Lady or the Tiger* (Stockton, 1882), where a man has a choice of two doors, behind one door is the lady and life and behind the other is the tiger and death, the uncertainty is the same as for the penny-matching game (one bit) but the value of knowing which door leads to the tiger is much greater than the value of half a penny. Accordingly, in signalling theory, the same quantity of information can differ considerably in value. This has important ramifications for an organism's response to environmental signals, given that the function of adaptive developmental plasticity is to improve health and/or fitness. This concept of responsiveness to signals is discussed in greater detail in Section III.4.

(*b*) *Quantifying epigenetic information*

(*i*) *Mechanics of DNA methylation*

We focus on DNA methylation as a mitotically heritable signal that transmits information about the environment early in life to affect an organism's phenotype later in life. We recognize that histone modifications and small non-coding RNAs also influence gene expression without changing the nucleotide sequence, but we will not address those mechanisms here.

In vertebrates, DNA methylation is the covalent addition of a methyl group to the fifth carbon of the pyrimidine ring of a cytosine base that belongs to a cytosine-phosphate–guanine (CpG) dinucleotide pair (Razin & Riggs, 1980). Details of the DNA methylation reaction are shown in Fig. 1. DNA methylation regulates gene expression by two primary mechanisms (Klose & Bird, 2006; Li & Bird, 2007; Bogdanovi & Veenstra, 2009). First, methylation may physically interrupt protein–DNA interactions by blocking transcription factors from binding to the nucleotide sequence (Watt & Molloy, 1988; Campanero, Armstrong & Flemington, 2000). Second, methylated CpG sites preferentially recruit protein complexes, which may alter chromatin structure and modify transcription (Nan *et al.*, 1998; Weaver *et al.*, 2014).

The mechanisms by which DNA methylation is established and its role in gene regulation were first proposed in 1975 (Holliday & Pugh, 1975; Riggs, 1975) and have since been a topic of great interest in biology. In brief, the majority of mammalian *de novo* CpG methylation occurs during early development following two genome-wide demethylation events, and subsequent re-establishment of methylation marks that depend on both genetic instructions and environmental conditions (Reik, Dean & Walter, 2001; Faulk & Dolinoy, 2011). The DNA methylation reaction is catalysed by a family of proteins known as DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B, all of which interact with DNA, RNA, and other proteins preferentially to methylate certain CpG regions while leaving other regions unmethylated (Goll & Bestor, 2005; Klose & Bird, 2006). The addition of methyl groups by DNMTs can enhance, reduce, or maintain gene expression in response to environmental factors (Bird, 2002; Jaenisch

& Bird, 2003). Methylation can also be removed from CpG sites *via* ten-eleven translocation (TET) enzymes (Kohli & Zhang, 2013). Coupled with DNMT activity, TET enzymes allow for more dynamic coordination of epigenetically controlled gene expression.

(*ii*) *DNA methylation as a signal*

We consider an epigenetic signal as a cluster of CpG sites in which DNA methylation corresponds to bits of information. Clusters of CpG sites that occur at high densities, often in the promoter region of genes, are referred to as CpG islands (Bird *et al.*, 1985; Illingworth & Bird, 2009) and changes in DNA methylation at CpG islands have potential to alter chromatin structure and influence gene expression (Bird, 1986; Deaton & Bird, 2011). Flanking either side of CpG islands are the slightly less GC-rich CpG island shores (Irizarry *et al.*, 2009), followed by even more distally located CpG island shelves (Bibikova *et al.*, 2011), which can be variably methylated and may also be associated with developmental differences in gene expression. Considering a genomic region that includes CpG clusters as a signal, we view each dinucleotide pair as a potential CpG site, and assume that all CpG sites can be in one of two states, methylated or unmethylated. Therefore, each CpG site may be viewed as an information-storage position that can take on values of 0 (unmethylated) or 1 (methylated). Collectively, a CpG cluster represents a binary sequence, which is similar in structure to the lines of bits in basic computer code, and that can influence gene expression.

The quantity of information in an epigenetic signal varies. In a section of DNA of fixed length, where n = number of nucleotides, there are 0 to $n/2$ CpG dinucleotide pairs. Considering that methylation status of any particular CpG site is binary, a single CpG site may function as an on/off switch *via* direct blocking or dim gene expression by reducing the probability that a transcription factor binds to the DNA. The presence of multiple CpG sites in the same section of DNA may allow for multiple combinations of 'on' and 'off' that together function like bytes of information in computer code. As the number of CpG sites and the quantity of information within an epigenetic signal increases, the number of outcome combinations increases exponentially, which may contribute to the precision of gene regulation in the same way that the arithmetic precision of digital computers can increase with the byte length of the central processing unit (CPU). In a biological context, DNA methylation of a CpG site in a single cell may physically block a transcription factor from accessing the domain within which the CpG site is located, thereby effectively turning off transcription in that specific cell. Conversely, removal of the methyl group from that same CpG site would allow the transcription factor to bind, and the cell could proceed with RNA transcription. The quantity of information based on methylation status of multiple cells within a tissue, even at a single CpG site, is measured as the average of binary methylation status (yes/no) across all cells. The potential phenotypic variation that results from an epigenetic signal increases as we consider multicellular tissue organization, multiple CpG sites, and higher-order interactions of DNA with methyl-sensitive proteins and chromatin folding mechanisms that can affect transcription across a continuum.

The value of a single bit *versus* combinations of bits of information in an epigenetic signal depends on how that information influences the organism's phenotypic response, and the extent to which that response is expected to enhance fitness. In the following sections, we expand upon this idea by reviewing the parts of a signal system, concepts of signal reliability, and the adaptive value of the receiver response in the form of developmental plasticity. However, before we continue, it is important to acknowledge some simplifying assumptions that we make in order to focus on DNA methylation as an example of an epigenetic signal. Specifically, the role of DNA methylation in relation to gene expression is complex and context dependent (Jones, 2012), but we will proceed with the generalization that higher promoter CpG methylation results in lower expression of the corresponding gene, whereas lower CpG methylation enhances expression (Li & Bird, 2007; Siegfried & Simon, 2010). For simplicity, we will not discuss the effects of transitional methylation chemical configurations, like hydroxymethylcytosine (Tahiliani *et al.*, 2009), which often occur around transcriptional start sites and enhancers and may be important for determining phenotypes (Yu *et al.*, 2012). We also recognize but do not formally address the fact that there may be correlations in the methylation states of neighbouring and/or functionally related CpG sites, which violates an assumption of information theory that each storage position is independent of other storage positions. However, accounting for the complex interrelations among CpG sites is beyond the scope of this review.

(2) Basic signal system design

In his classic paper, Shannon (1948) developed a schematic for a general communication system, which we have modified slightly to enhance clarity (Fig. 2). In Fig. 3 we adapt Shannon's representation to illustrate our conceptualization of epigenetic mediation of adaptive developmental plasticity (Bateson *et al.*, 2004; Gluckman, Hanson & Spencer, 2005*b*) as a noisy communication system.

An organism's response to environmental stimuli *via* epigenetic mechanisms fit neatly into this signal system paradigm. As a signal sender, an organism encodes information from the environment, and transmits it over the course of development as DNA methylation marks that are analogous to bits in a byte. At a future time point, the organism is the signal receiver, who decodes the signal and uses the information to guide its phenotypic response (Fig. 3B).

(3) Signal reliability

The motivation to understand signal reliability is to elucidate how signals permit communication (Hasson, 1994, 1997; Hurd & Enquist, 2005; Wiley, 2006). When considering signal reliability, we focus on the signal sender (the organism at present), properties of the signal, and a signal receiver (the organism in the future) (Bradbury & Vehrencamp, 2011). Successful communication occurs when the signal is efficacious enough to reach the receiver (efficacy) and the information is meaningful to the receiver (content) (Guilford & Dawkins, 1993). Signal efficacy is the capacity of the signal to transmit from the sender and be detected by receiver (Guilford & Dawkins, 1993), and depends on the signal's physical structure as well as properties

of the signal channel (e.g. distance between sender and receiver and background noise) that influence signal detectability and discriminability. On the other hand, signal content refers to the actual message and the ability of the receiver to understand the message in order to reduce uncertainty or improve prediction.

(*a*) *Signal efficacy*

Efficacy in biological communication depends on the signal-to-noise ratio (Beal, 2015). There are three aspects to consider in regard to signal efficacy: (1) the signal's structure and intensity, (2) internal system errors (noise), and (3) external errors (background noise) (Guilford & Dawkins, 1991; Endler, 1992).

To start, we can use an example of people talking through a string and tin-can telephone to conceptualize signal efficacy. Person A speaks "Watch out below," into a tin can. The auditory signal arrives at the tin can of the receiver, Person B, and the message is decoded. A louder spoken message improves efficacy by increasing the amplitude of the sound waves. When thinking of signal efficacy, for example, in regard to an epigenetic signal communicating information about the organism's nutritional environment, we propose that, at an initial time point, an organism (the signal sender) encodes information about its current environment [$E_1(\bullet)$ in Fig. 3B] as DNA methylation marks on CpG sites [$M_1(\bullet)$] that are transmitted to the future. At a later time point, the organism (now the signal receiver) reads the methylation marks [$M_F(\bullet)$] and translates them into a phenotype [$T_F(\bullet)$], which might or might not be a good match for the

adult environment [$E_F(\bullet)$]. For example, in a nutrient-poor early-life environment such as that caused by famine [$E_1(p)$], the young organism encodes the information about its current environment by decreasing methylation of gene regions involved in growth and metabolism [$M_1(p)$]. Then, the message is transmitted to later in life with imperfect fidelity due to internal process errors, as discussed in the next section. The older organism decodes the epigenetic signal [$M_F(p)$], and develops a metabolically efficient ('thrifty') phenotype [$T_F(p)$] in anticipation of a nutrient-poor environment [$E_F(p)$]. In the next two sections, we describe the process of transmitting epigenetic signals, specifically focusing on the potential impact of internal and external noise in the epigenetic communication channel.

(*i*) *Internal process errors: epigenetic fidelity*

Internal process errors in a signal system reduce signal fidelity. In the tin-can telephone example, the length of the string affects the integrity of the auditory message. A shorter string will yield lower attenuation of sound waves than a longer string, resulting in a more-conserved (e.g. higher fidelity) message decoded by the signal receiver at the later life stage. Similarly, DNA methylation is subject to internal copy mechanism errors that act as noise, ultimately degrading fidelity of the epigenetic signal during transmission. Once established, DNA methylation marks are clonally inherited as part of DNA replication during each cell division (Bestor & Tycko, 1996; Chen & Riggs, 2005). The newly formed DNA is asymmetrical and hemi-methylated, so reliable propagation of the epigenetic signal requires restoration of complementary methylation.

The protein NP95, also known as UHRF1 [ubiquitin-like with plant homeodomain (PHD) and ring finger domains], has an affinity for hemi-methylated DNA and recruits DNMT1 to restore complementary methylation (Ooi & Bestor, 2008). This process of methylation maintenance results in faithful transmission of epigenetic signals with over 95% accuracy in both theoretical (Pfeifer *et al.*, 1990; Riggs & Xiong, 2004) and empirical models (Laird *et al.*, 2004). However, fidelity of methylation maintenance is not guaranteed and random errors, known as epigenetic drift, can occur (Fraga *et al.*, 2005; Wong, Gottesman & Petronis, 2005). Twin studies have shown that, despite shared genetics and prenatal environment, random errors in epigenetic signals arise during the aging process and contribute to phenotypic divergence between individuals over time (Fraga *et al.*, 2005; Martin, 2005; Fraga & Esteller, 2007). The process of epigenetic drift is caused by the failure to recapitulate DNA methylation faithfully during cell division, and emphasizes the role of stochasticity in modifying the phenotypes of organisms that transmit epigenetic signals across many cell divisions and over long time periods (Wong *et al.*, 2005; Shibata, 2009). The extent to which epigenetic signals are subject to drift, and how much internal error affects signal reliability are likely to have important implications for developmental trajectories and adult-onset diseases, as well as for the evolution of predictive adaptive responses (PARs).

Notably, when considering epigenetic signal efficacy, it is important to keep in mind that genetics also plays a role. Genomic sequence variants may limit the available CpG sites for information storage, and background genetic variation may alter the form and function of

downstream proteins responsible for DNA methylation maintenance (Bjornsson, Fallin & Feinberg, 2004). For example, the degree of global methylation stability over time (which likely includes changes due to drift) is more similar within than between families, suggesting a genetic basis for the accumulation of epigenetic errors over time (Bjornsson *et al.*, 2008). Genetic variation could thus hypothetically alter epigenetic drift trajectories to affect signal reliability by contributing noise to the system.

(*ii*) *External process errors: environmental perturbations*

Epigenetic signals are also subject to external sources of error. Specifically, environmental perturbations occurring between the initial developmental time point of interest early in life and the later time point when phenotype is assessed, can introduce noise and exacerbate random errors in the epigenetic signal system [forcing differences between $M_1(\bullet)$ and $M_F(\bullet)$]. In our tin-can telephone example, a spoken signal will be clearer in a quiet room, where sound waves are not perturbed by ambient noise, than in a room full of conversing people.

To illustrate the concept of external process errors, we present a few examples from the human literature. A study of monozygotic twins found greater variability in the epigenomes of adult than children twin pairs, as well as greater differences between the epigenomes of adult twins who grew up in different than in similar environments (Fraga *et al.*, 2005). The latter finding suggests that, in addition to internal noise (e.g. imperfect replication of methylation marks as part of multiple cell divisions), signal efficacy is also susceptible to external noise (e.g.

environmental perturbations like toxicants, hormones, nutrition etc.). Early-life exposure to environmental toxicants can influence DNA methylation and ultimately, increase risk of adult disease (Dolinoy, Huang & Jirtle, 2007*b*). Broadly speaking, when environmental factors like toxicants (Kundakovic *et al.*, 2013) or synthetic hormones (Crudo *et al.*, 2012) alter expression of methylation maintenance machinery, the effect may be to alter DNA methylation patterns and perhaps also to change the rate of epigenetic drift. For instance, prenatal exposures to lead (Faulk *et al.*, 2014) and bisphenol A (BPA) (Kochmanski *et al.*, 2016) are associated with altered age-related methylation changes. Such findings indicate that a variety of external factors may compromise signal efficacy by altering the rate of epigenetic drift (Kochmanski *et al.*, 2017). However, the extent to which the environment is simply a source of external noise, rather than a force that elicits deterministic changes in the epigenome, are two separate concepts which may be difficult to disentangle empirically.

(*b*) *Signal content*

The second part of signal reliability is the meaning of the message (Guilford & Dawkins, 1991; Maynard Smith & Harper, 2003). In our conceptualization (Fig. 3) the meaning of the signal (i.e. the message), which is encoded as $M_F(\bullet)$, is translated into trait $T_F(\bullet)$. Above, we focused on the potential roles of internal and external noise in degrading signal reliability. Signal content may also be unreliable if either the message or the environment changes over the course of transmission. We thus divide potential threats to signal content into two categories: (1)

deterministic changes to signal content [e.g. potentially adaptive, population level changes to $M_1(\bullet)$ and $M_2(\bullet)$ that result in $M_F(\bullet)$], and (2) environmental instability [e.g. probabilistic differences between $E_1(\bullet)$ and $E_F(\bullet)$, given $E_1(\bullet)$ and $E_2(\bullet)$].

(*i*) *Deterministic changes to signal content*

During vulnerable windows of development, such as the prenatal period, infancy and puberty, the epigenome is particularly sensitive to environmental exposures (Dolinoy *et al.*, 2007*a*; Faulk & Dolinoy, 2011). Accordingly, these are prime timeframes for encoding and modifying epigenetic messages in response to the environment, allowing for potentially adaptive plasticity. The environment, $E_1(\bullet)$, at an initial time point, provides information that is encoded into the epigenome $M_1(\bullet)$, which may improve the organism's performance in its future environment, $E_F(\bullet)$; (Fig. 3). Later in ontogeny, another environmental factor, $E_2(\bullet)$, might modify the epigenome $M_2(\bullet)$. The combination of environmental factors will each contribute (additively or multiplicatively) to the future epigenome $M_F(\bullet)$, which is then decoded as information used for a phenotypic response $T_F(\bullet)$. Because epigenetic signals transmit through a sequence of developmental windows, environmental information entering through a later window might modify the message from an earlier window. For example, animal models indicate that maternal peri-conceptional and gestational nutrition affect offspring phenotype through epigenetic mechanisms (Waterland *et al.*, 2006; Sinclair *et al.*, 2007; Carlin, George & Reyes, 2013), but also that offspring DNA methylation patterns can remain responsive to nutrition over the life

course (Cordero *et al.*, 2013), particularly during developmental life stages characterized by rapid growth or development and/or hormonal fluctuation, such as during infancy, puberty, and pregnancy. The addition or removal of DNA methylation in response to multiple environmental exposures that occur throughout development may compromise signal reliability by changing the meaning of the original message.

Changes in DNA methylation can also affect signal content by inducing changes in the underlying genetic code. First, the addition of methylation can lead to deamination of methylated cytosine into thymine, resulting in a cytosine-to-thymine point mutation (Bird, 1980), and can reduce the number of CpG sites, leaving the signal depleted of information-storage positions (Simmen, 2008). Second, removal of methylation can lead to activation of transposons, which include mobile segments of remnant viral DNA that can propagate themselves throughout the genome *via* cut-and-paste or copy-and-paste mechanisms (Finnegan, 1989; Slotkin & Martienssen, 2007). While the former reduces the storage potential of epigenetic signals due to removal of CpG sites, the latter may increase information storage potential by reseeding CpG sites. Thus, both changes in CpG site density due to nucleotide mutations or transpositions that are sensitive to methylation status, and changes in DNA methylation in response to environmental exposures, can influence epigenetic signal content.

(*ii*) *Environmental instability*

Content-related signal reliability also depends on stability of the environment. Both long transmission distances (i.e. time) and unstable environments can make future operating environments too unpredictable to anticipate adaptively. The likelihood that $E_1(\bullet)$ and $E_F(\bullet)$ are the same is based on the conditional probability of $E_F(\bullet)$, given $E_1(\bullet)$ and $E_2(\bullet)$; (Getty, 1996 and Fig. 3A). For example, an organism in a nutrient-restricted environment encodes a DNA methylation pattern that emphasizes the need for a thrifty metabolism. Later in life, the organism receives the methylation signal and responds with gene expression that produces a thrifty metabolism. If the signal indicating a food-deprived environment from early life accurately captures the later-life food environment, then the signal's content improves the organism's performance. On the other hand, in the event of a mismatch between the food environments in early and later life, the thrifty phenotype may be maladaptive in the later-life environment (Godfrey *et al.*, 2007). Whether or not an environment changes over time is independent of the signal transmission process, but together signal reliability and environmental instability determine whether or not a mechanism can evolve that accurately anticipates a probabilistic future environment and develops the appropriate adaptive phenotype for that environment.

(4) Receiver response: signal detection theory

Developmental plasticity is a form of receiver response, as it represents the capacity of an organism to modify its phenotype based on information about its environment previously encoded as an epigenetic signal. In a biological signal system, an organism can either respond to

or ignore a signal using a set of rules, referred to as decision criteria (Wiley, 2006; Anderson, 2015). Decisions are based on whether or not the signal improves prediction, and the probable costs and benefits associated with a response. Given the two response options (respond or reject) there are four possible outcomes that represent the match between receiver response $T_F(\bullet)$ and the environment $E_F(\bullet)$ (Fig. 4A). These four outcomes can be mapped as a two-by-two contingency matrix: correctly respond to a signal, correctly reject noise, incorrectly respond to noise, and incorrectly reject a signal (Wiley, 2006; Anderson, 2015). This contingency table can be used to assess a receiver response, where that response is a discrete phenotypic state that depends on both the reliability of an epigenetic signal and the ability of the receiver to decode the message.

As part of this assessment we can quantify two useful epidemiological measures of predictability, sensitivity and specificity. Sensitivity is the ability to respond to a signal when it is appropriate to do so, and specificity is the ability to reject a signal when it is inappropriate (Rothman, Greenland & Lash, 2008). Each cell in the contingency table is effectively an area under curves representing noise and signal above or below the decision criterion (Fig. 4B). The phenotypic response can also be described continuously by integrating the probability distribution functions for noise and signal between the limit of the decision rule (the value of the *x*-axis intersection) and infinity in positive or negative directions. Then, comparing the areas under the curves with a signal-to-noise ratio we can generate receiver operating characteristic (ROC) curves to assess the predictive capacity of an epigenetic signal, and even identify an

optimal threshold at which the signal-to-noise ratio should elicit a response (developmental plasticity). By comparing the noise and signal distributions alongside the contingency table or ROC curves, we can evaluate how epigenetic signal reliability influences prediction, and the probability with which receiver response results in a match between the phenotype and environment.

(*a*) *Receiver response based on reliability*

Receiver response depends on signal efficacy (e.g. process errors) and content (e.g. the message). Reduced signal efficacy is synonymous with increased internal and external errors in the signal channel and accordingly, more variance in the noise and signal distributions (Fig. 4C). For example, the longer the time between signal establishment and reception of the signal, the greater the potential for internal errors in methylation (i.e. more epigenetic drift) and accordingly, the greater the variance in the signal distribution. Likewise, external errors caused by environmental perturbations increase the variance in the noise distribution. Ultimately, higher rates of internal and external errors lengthen the tails of the signal and noise distributions, respectively, increasing the degree of overlap between the distributions to reduce signal discriminability (Fig. 4C).

Receiver response also depends on reliability of signal content. Here, the mean of the signal distribution represents the signal's content, and mean of the noise distribution represents background noise content (e.g. any background unrelated to the signal's message). If we imagine

a collection of epigenetic signals, those that have a number of methylated CpG sites closest to the signal mean and furthest away from the background noise mean will have the clearest message, and thus, are expected to influence an organism's phenotype most consistently. Factors that shift the signal mean towards the mean of the noise distribution, such as changes in DNA methylation that result from conflicting information from multiple environmental sources, increase the overlap between the two distributions (Fig. 4D). Increasing overlap in signal and noise distributions obscures the message and reduces the probability that a receiver will benefit by acting on the message, so a positive response is increasingly likely to be a false response.

Considering together the effect of signal efficacy and content on receiver response in our thrifty phenotype example, correctly anticipating a nutrient-poor adult environment [T_2(p) matched to E_2(p)] corresponds to a 'correct response' (Getty, 1996; Fig. 4A). Correctly anticipating a nutrient-rich adult environment [T_2(r) in E_2(r)] is a 'correct reject'. The two scenarios depicted in Fig. 4C and D both decrease discriminability between signal and noise, decreasing the probability that a positive developmental response to an early signal will adaptively match the later phenotype to the later-life environment.

(*b*) *Receiver response based on signal value*

The value of a receiver response, and by extension, the value of the signal, depends on whether a particular decision to respond and the resultant phenotype are adaptive or maladaptive in the organism's later-life environment. We can quantify the value of an organism's phenotypic

response to an epigenetic signal using the fitness trade-off matrix (Fig. 5). The fitness (ω) of a communication system for making PARs depends on the trade-offs associated with the receiver response, as well as signal reliability and environmental stability within the organism's lifetime. This means that optimization of the decision-making process based on reliability alone is not always the best strategy. Flexibility in receiver response reflects the ability of an organism to balance trade-offs between signal reliability and signal value.

Assuming that the decision criterion can adapt or evolve, an organism's responsiveness to environmental signals should vary with the costs of errors (false reject, false respond) as well as the benefits of correctly rejecting and correctly responding. When the cost of rejecting a true signal is high relative to responding to noise, then lowering the criterion for responding is optimal; a scenario we refer to as reactive plasticity (Fig. 5) (Getty, 1996). For example, an organism born in a nutrient-limited environment is unlikely to survive unless growth is restricted. Alternatively, although growth restriction in a nutrient-abundant environment is not ideal and may lead to metabolic disease, it is not as costly as starvation. Here, the decision criterion would shift left such that the organism is more likely to respond by growth restriction, even if the epigenetic signal is weak.

Alternatively, the decision criterion might shift right, limiting responses to signals that indicate only the most extreme environments (Fig. 5). When responding to noise is more costly than rejecting a signal, an extremely high response criterion is appropriate. Conspicuous epigenetic signals, like genome-wide demethylation induced by extreme environmental stressors,

could induce genetic and phenotypic variation by releasing transposable elements from their repressed state (McClintock, 1984; Hunter *et al.*, 2014). More biological variation *via* transpositions and other mutations could be an adaptive process, possibly enabling a small portion of the population to survive (Shapiro, 2017). However, the risks associated with genome-wide destabilization are also extremely high given that genomes are the product of a long evolutionary history. Such high-stake situations should favour a very high response criterion in which organisms overcompensate by rejecting noise at the expense of potentially rejecting information; a strategy that can be thought of as 'reluctant plasticity'.

IV. MERGING HYPOTHESES REGARDING DEVELOPMENTAL PLASTICITY WITH LIFE-COURSE MODELS

There are a number of hypotheses pertaining to biological pathways underlying developmental plasticity and the potential for a match (or mismatch) between an organism's phenotype and its environment: the predictive adaptive response hypothesis (Bateson *et al*., 2004; Gluckman *et al*., 2005*b*), the thrifty phenotype hypothesis (Hales & Barker, 2001), and the DOHaD hypothesis (Gillman, 2005). Each of these shares the view that environmental stimuli during early development can alter an organism's later-life phenotypes. In this section, we briefly describe theoretical models from life-course epidemiology, which is a methodological framework used to conceptualize and test biological pathways linking early-life experiences and exposures to health throughout the life span. Although concepts from this field have only been systematically applied

in human studies, they are relevant to developmental plasticity observed in other organisms studied by evolutionary developmental biologists.

There are two broad categories of life-course models: critical period models and risk accumulation models (Kuh *et al.*, 2003). Generally speaking, critical period models posit that experiences during sensitive developmental windows early in life lead to permanent changes in phenotype that are not substantially altered by subsequent experiences. Metaphorically, there is a distinct window of responsiveness to environmental information. After it closes, development is canalized. In Fig. 3, midlife signals [$M_2(\bullet)$] are ignored. This model aligns with the polyphenism observed in the desert locust described in Section II.1. Indeed, after establishment of methylation marks during the juvenile stage, the morphological and behavioural phenotypes of the locust are established for life. On the other hand, risk accumulation models suggest that the effects of environmental factors or risk exposures accumulate gradually, and may interact (e.g. later exposures may exacerbate or mitigate health effects of previous exposures) over an organism's life span (the window stays open and midlife signals [$M_2(\bullet)$] significantly modify the early signal [$M_1(\cdot)$]). An example of this is prenatal BPA exposure and methyl-donor supplementation in Agouti mice; here nutrient supplementation mitigates the hypomethylating effects of BPA exposure on the A^{vy} region, indicating an interaction between BPA exposure and nutrient supplementation (Dolinoy *et al*., 2007*b*). Although nutrient supplementation attenuates the adverse impact of BPA, the reverse is also possible; in other cases subsequent environmental

factors exacerbate adverse effects of earlier exposures (Hahn-Townsend *et al.*, 2016), potentially *via* epigenetic modifications.

Assessing epigenetically mediated developmental plasticity within both a signalling system and life-course epidemiological framework is valuable for two reasons. First, a clear conceptualization of the temporal relations among exposures, mediators, and outcomes of interest using life-course epidemiology models will directly inform study design. Second, superimposing signalling system concepts onto life-course models can help to identify process error in signal transmission and formulate analytical strategies to parse out the impact of different types of variation (e.g. stochastic *versus* deterministic) on relationships among an organism's early environment, DNA methylation marks, and the organism's future environment and phenotype.

When considering an adaptive epigenetic signalling system that follows critical period models, an epigenetic signal is encoded during gestation or infancy, and that message directly affects the organism's future phenotype. In an error-free signal system, a study testing this hypothesis would require: (1) assessment of the environmental factor during an initial developmental period, (2) assessment of the epigenetic signal at any point in time following the developmental period of interest, assuming it remains stable after initial establishment, (3) assessment of the phenotype in its later-life environment, and (4) assessment of the correlation between early and late environments. An example is methylation of imprinted genes, like *IGF2*, which is established in gametes prior to conception and remains unchanged throughout

development (Barlow & Bartolomei, 2007). Accordingly, an analytical strategy could be a standard mediation analysis where the nutritional exposure is the independent variable, *IGF2* methylation is the mediator, and adult phenotype is the dependent variable. If DNA methylation is the sole mechanism linking early nutrition to future phenotype, then inclusion of *IGF2* methylation in the model as a mediator would wholly attenuate the regression ^{2} -estimate for early nutrition. Although the simplicity of critical period models is appealing, it is likely that methylation marks, including those on imprinted genes, are subject to process errors in the form of epigenetic drift, which may contribute to endogenous plasticity (Stamps, 2016), and/or deflection, which incorporates external perturbations as recently shown in a mouse model (Kochmanski *et al.*, 2016).

Risk accumulation models suggest that both DNA methylation signals, and later-life phenotypes, are affected by the accumulation of, and interactions among, environmental stimuli across development. One example of this model is that of prenatal BPA exposure and methyl-donor supplementation in Agouti mice described above (Dolinoy *et al*., 2007*b*). When designing a study to test this model, one might be interested either in examining the independent effect of exposures during specific developmental periods, or quantifying the cumulative effects on phenotype of exposures throughout the life course. Although data collection and study design for both are similar, the appropriate analytical strategy differs. We have described modelling techniques in greater detail in Laubach *et al*. (2017). In brief, testing accumulation of risk models requires appropriate partitioning of phenotypic variances due to deterministic and stochastic

processes, as both are hypothesized to affect DNA methylation over time. This may be done using mediation analysis to isolate direct effects of specific developmental stages, linear mixed models to capture both deterministic changes to DNA methylation *via* main effects and stochastic individual variability *via* empirical best linear unbiased predictors (EBLUPs).

V. CONCLUSIONS

(1) Epigenetic marks, such as DNA methylation, may serve as mechanistic links between environmental factors that organisms experience during development and their resultant phenotype, thereby enabling adaptive developmental plasticity – a phenomenon that is well recognized in both evolutionary developmental biology and human health.

(2) We used a basic signal system design to conceptualize ways in which DNA methylation can act as a signal relaying information about an organism's early-life environment to its future self in order to improve fit between future phenotype and environment. Considering epigenetic marks as signals provides a framework within which to identify potential sources of external and internal information-transmission errors, develop appropriate study designs based on biological plausibility, and parameterize statistical models to reflect biological processes accurately.

(3) The evolutionary maintenance of adaptive developmental plasticity *via* epigenetic signalling represents a proximal mechanism for organisms with fixed genomes to respond adaptively to environmental stimuli within their lifetimes. This has implications for human health and for evolutionary theory. We hope that this paper facilitates an increasingly open and

interdisciplinary approach to studying epigenetically mediated developmental plasticity that will improve understanding of both evolutionary developmental biology and determinants of human health and disease.

(4) Given the complexities of an epigenetic signal system where the signal is subject to change over time, use of appropriate statistical techniques to capture this nuance is critical. An intuitive frequentist approach would be a standard mediation analysis where the predictor is the environmental factor of interest during early life, the outcome is phenotype at a later life stage, and the mediator is change in DNA methylation over time, parameterized as trajectories. This strategy is an improvement upon traditional mixed-model approaches (or, simply averaging DNA methylation over time), as it considers the potential influence of temporal variability in DNA methylation. However, a limitation of this approach is that the trajectories do not distinguish between deterministic and stochastic modifications of methylation marks, and thus may yield less-reliable estimates of association.

(5) Looking forward, we propose use of a Bayesian decision-theoretic approach to model phenotypic plasticity over the course of development. One could model prospective changes in DNA methylation in response to a series of environmental factors that are experienced over the course of ontogeny, in which the DNA methylation at a given point in time is conditional on methylation at a previous life stage. As an organism develops, environmental factors can have deterministic effects on the DNA methylation mark of interest, which represents an 'update' from the previous methylation state. In this example, the posterior distribution for the estimate

representing the relationship between the environmental factor of interest and DNA methylation at the earlier life stage would serve as the prior for the estimate of association representing the relationship between the environmental factor later in life and the methylation mark (Stamps & Frankenhuis, 2016). Using this type of model, it is possible to assess how a series of previous environmental experiences modify the epigenetic signal. Ultimately, this may enable more accurate statistical modelling of the relationships among early environment, DNA methylation, future environment and future phenotype.

(6) Going a step further, Bayesian stochastic process models may be used to partition variance further due to deterministic and stochastic influences on the relationship between an epigenetic signal and the resultant phenotype. Accounting for stochastic changes (e.g. drift and/or deflection) as well as deterministic ones is important, as they too may alter the epigenetic signal. Use of stochastic process models would allow us not only to account appropriately for deterministic variability in DNA methylation over time, but also, such models partition variance in change in DNA methylation due to stochastic variability, which encompasses both external and internal process errors (Bolker, 2008). These models have potential to improve accuracy of statistical methods used to capture the true relationships among early life exposures, epigenetic mechanisms, and future phenotype. In evolutionary developmental biology, such models would provide a better quantification of the phenotypic variation upon which selection acts – a fundamental premise of the field. In the field of human health and DOHaD, accurate estimates of association have direct implications for intervention strategies and health policy.

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Figure legends

Fig. 1. The DNA methylation reaction and one-carbon metabolism. Folic acid enters one-carbon metabolism as dihydrofolate (DHF), which is reduced to tetrahydrofolate (THF), which is converted to 5,10-methylene THF in a reaction catalysed by vitamin B6 and serine hydroxyl-methyltransferase. Vitamin B2, precursor to flavin adenine dinucleotide, is a cofactor to methylenetetrahydrofolate reductase in the conversion of 5,10-methylene THF to 5-methyl THF. Vitamin B12 is a precursor to methionine synthase, which is involved in the production of methionine and dimethylglycine (DMG) from homocysteine and betaine. Zinc is a cofactor to the DNA methyltransferases (DNMTs) in the transfer of the methyl group from S-adenosylmethionine (SAM) to the 5th carbon of cytosine. Demethylated SAM becomes S-adenosylhomocysteine (SAH), which is subsequently hydrolysed to homocysteine by adenosylhomocysteinase. Homocysteine can be recycled back to methionine with adequate methyl-donor (folate and choline) and methylation cofactor (vitamin B12, vitamin B6, vitamin B2, and zinc) micronutrients. Adapted with permission from Anderson *et al*. (2012).

Fig. 2. Shannon's original system design. Adapted from Shannon (1949).

Fig. 3. (A) A dynamic environment over time. E_I and E_F represent the early and later environments, respectively, which may be either nutrient poor (p) or rich (r). PR […] represents

conditional probability of a match (e.g. poor early-life environment/poor later-life environment) or mismatch (e.g. poor early-life environment/rich later-life environment). (B) An epigenetic signal system where environmental factors impact DNA methylation at multiple points in time across an organism's life course (M_1, M_2, M_F) depending on a nutrient-poor (p) or -rich (r) environment. Adult phenotype is represented as $T_F(p)$ or $T_F(r)$ reflecting the phenotypic response. Epigenetic drift and environmental perturbations (i.e. deflection) both contribute stochastic variability, or process noise, to the signal.

Fig. 4. (A) A depiction of signal detection theory and determinants of a matched or mismatched response where E_1 and E_F represent the early and later environments, respectively, either of which may be nutrient poor (p) or rich (r). (B) Distribution of noise and information in a signal system, and determinants of response to a signal. (C) Scenario of reduced efficacy. (D) Scenario of modified signal content.

Fig. 5. Alterations in decision rules based on signal value. E_1 and E_F represent the early and later environments, respectively, either of which may be nutrient poor (p) or rich (r). Fitness (ω) depends on the performance of a phenotype in its present environment. Organisms are expected to be more likely to show a phenotypic response when the fitness costs of a false rejection are highest and they are less likely to respond when the fitness costs of a false response are highest; thus the value of the information in the signal influences receiver response.

Figure 1

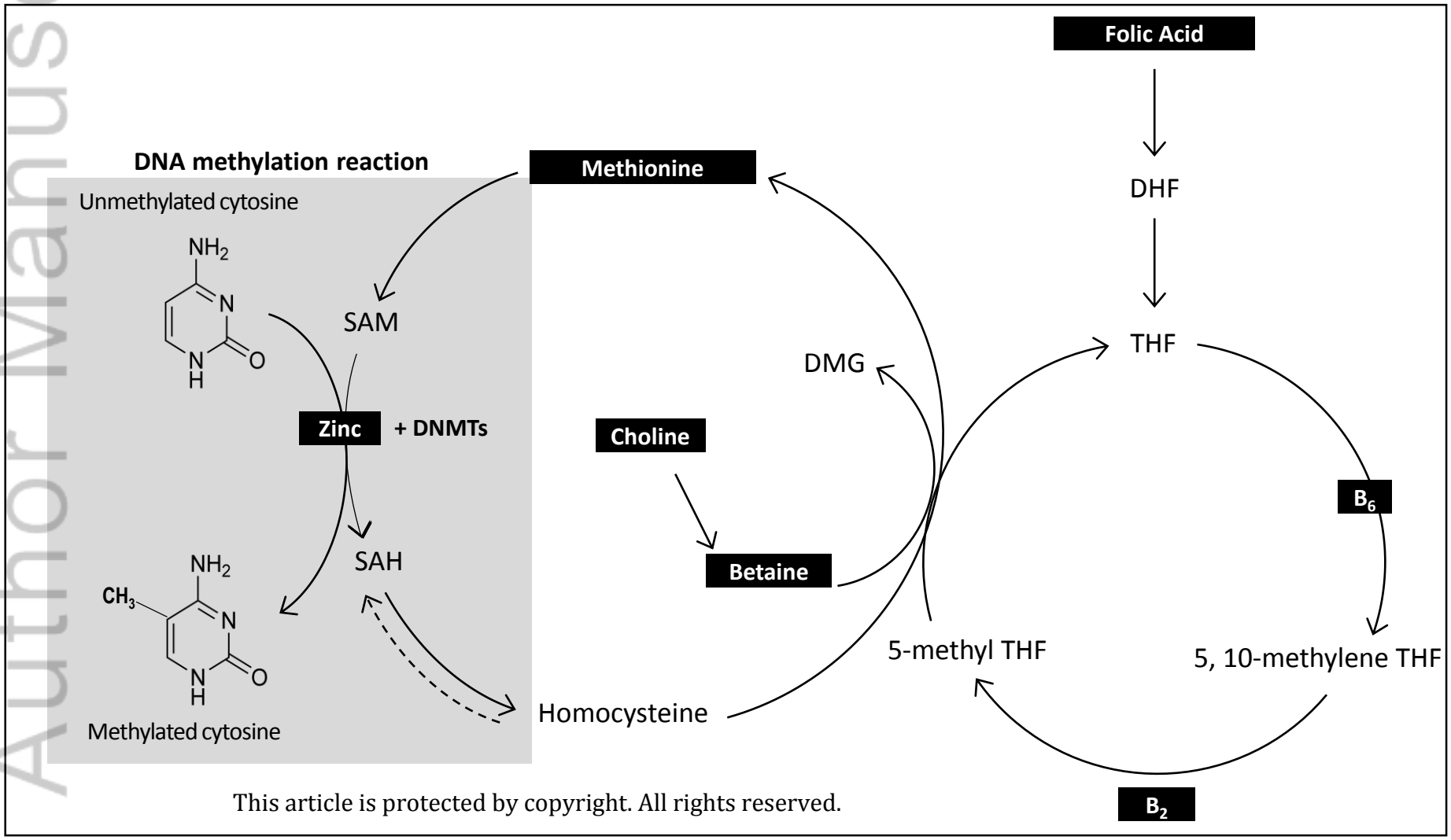

Figure 2

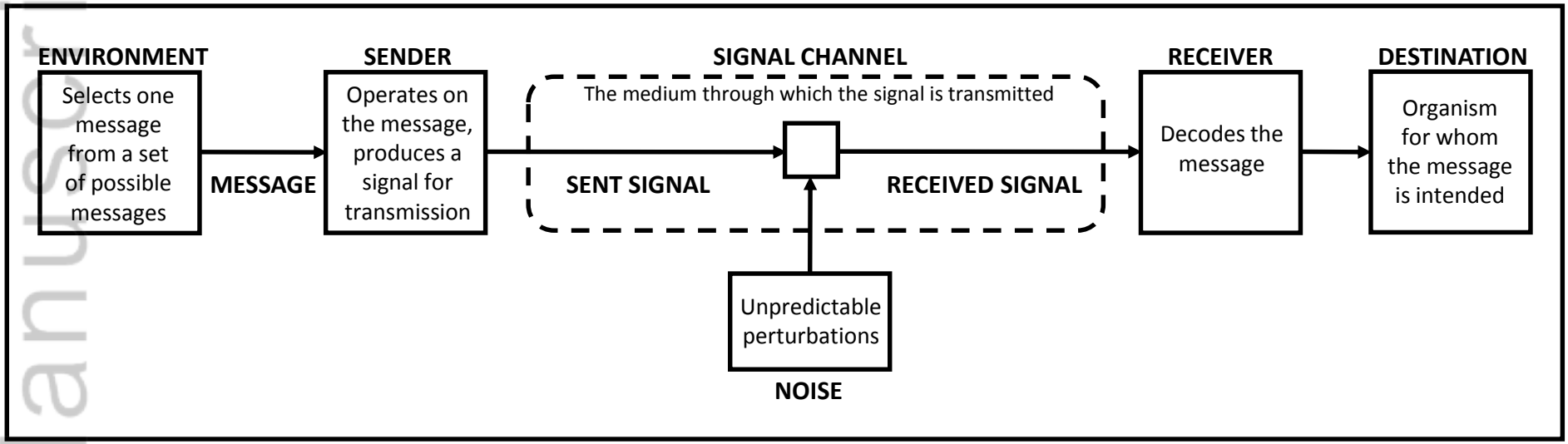

Figure 3

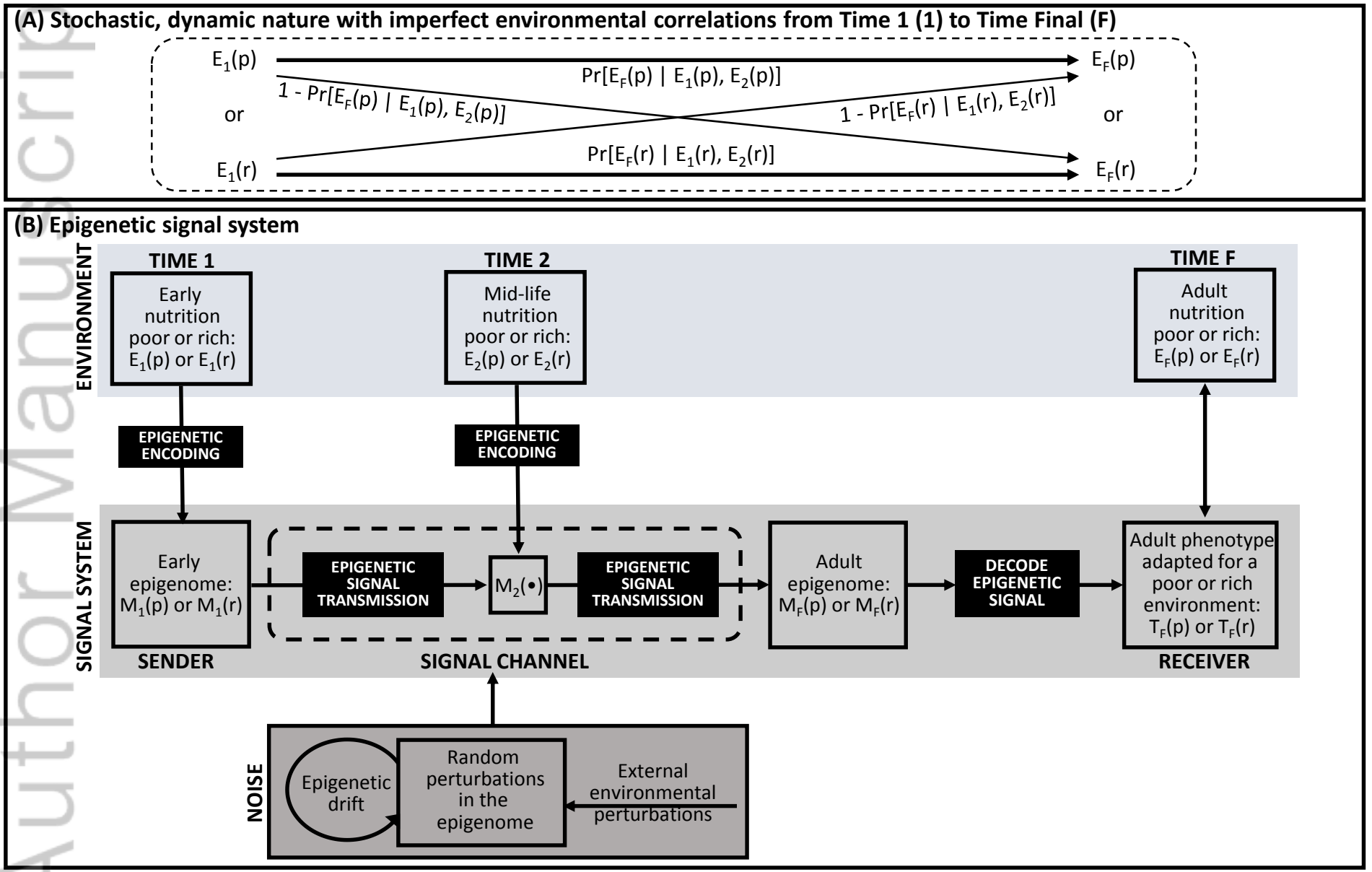

Figure 4

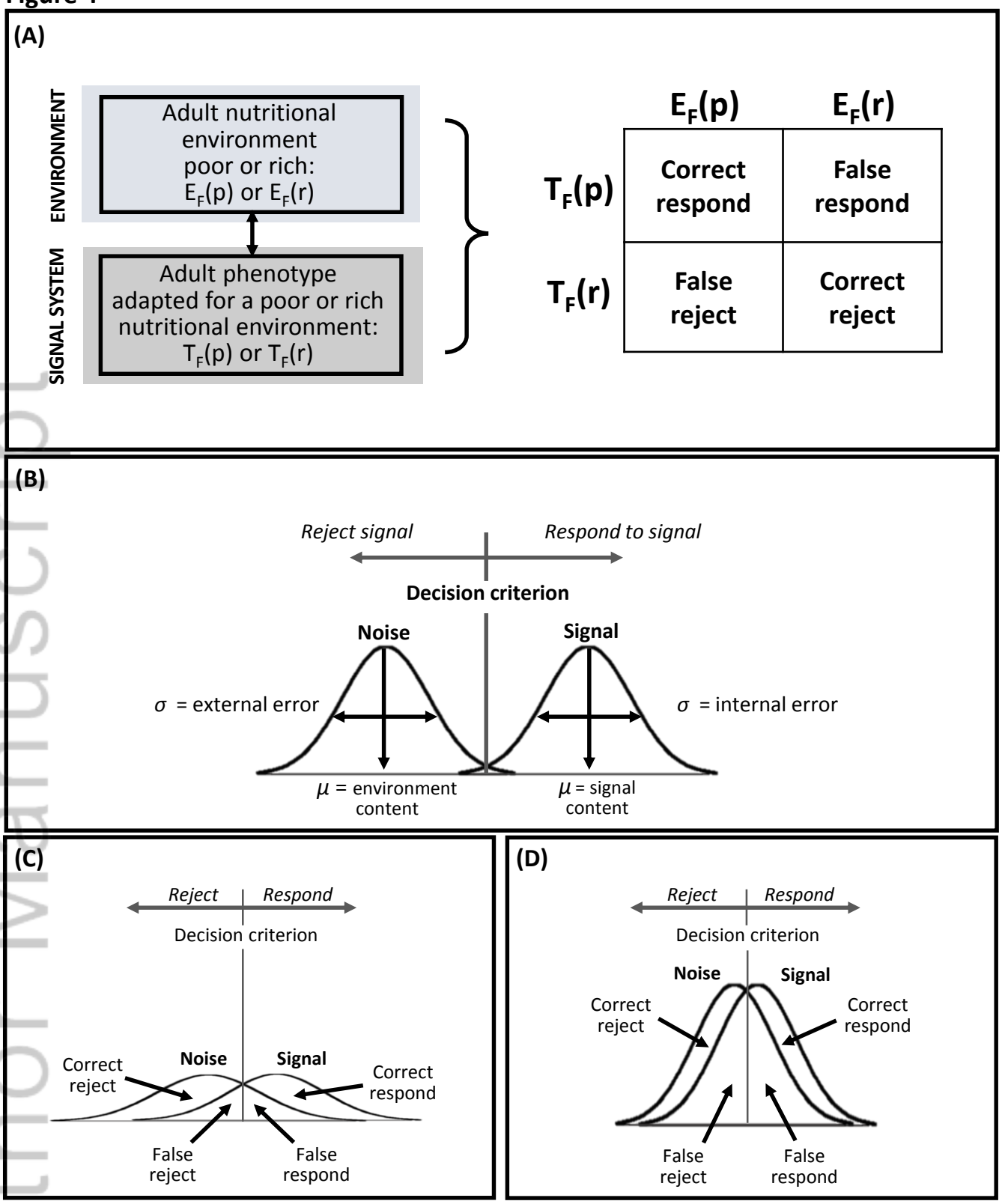

Figure 5