Review

Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences

GÜNTER VOGT

Faculty of Biosciences, University of Heidelberg, Im Neuenheimer Feld 230, D-69120, Heidelberg, Germany

(Email, gunter.vogt@web.de)

This article reviews the production of different phenotypes from the same genotype in the same environment by stochastic cellular events, nonlinear mechanisms during patterning and morphogenesis, and probabilistic self-reinforcing circuitries in the adult life. These aspects of phenotypic variation are summarized under the term 'stochastic developmental variation' (SDV) in the following. In the past, SDV has been viewed primarily as a nuisance, impairing laboratory experiments, pharmaceutical testing, and true-to-type breeding. This article also emphasizes the positive biological effects of SDV and discusses implications for genotype-to-phenotype mapping, biological individuation, ecology, evolution, and applied biology. There is strong evidence from experiments with genetically identical organisms performed in narrowly standardized laboratory set-ups that SDV is a source of phenotypic variation in its own right aside from genetic variation and environmental variation. It is obviously mediated by molecular and higher-order epigenetic mechanisms. Comparison of SDV in animals, plants, fungi, protists, bacteria, archaeans, and viruses suggests that it is a ubiquitous and phylogenetically old phenomenon. In animals, it is usually smallest for morphometric traits and highest for life history traits and behaviour. SDV is thought to contribute to phenotypic diversity in all populations but is particularly relevant for asexually reproducing and genetically impoverished populations, where it generates individuality despite genetic uniformity. In each generation, SDV produces a range of phenotypes around a well-adapted target phenotype, which is interpreted as a bet-hedging strategy to cope with the unpredictability of dynamic environments. At least some manifestations of SDV are heritable, adaptable, selectable, and evolvable, and therefore, SDV may be seen as a hitherto overlooked evolution factor. SDV is also relevant for husbandry, agriculture, and medicine because most pathogens are asexuals that exploit this third source of phenotypic variation to modify infectivity and resistance to antibiotics. Since SDV affects all types of organisms and almost all aspects of life, it urgently requires more intense research and a better integration into biological thinking.

[Vogt G 2015 Stochastic developmental variation, an epigenetic source of phenotypic diversity with far-reaching biological consequences. *J. Biosci.* **40** 159–204] **DOI** 10.1007/s12038-015-9506-8

1. Introduction

The phenotype is of outstanding importance in biology because it expresses individuality, interacts with the environment, and serves as target of natural selection (Rollo 1995; Schlichting and Pigliucci 1998; West-Eberhard 2003; Piersma and van Gils 2011; Jablonka and Lamb 2014). Despite intense research for more than a century, we are far from fully understanding how phenotypes are produced from genetic templates and how phenotypic variation is generated (Nanjundiah and Newman 2009; Pigliucci 2010; Hallgrímsson and Hall 2011a; Sozzani and Benfey 2011; Landry and Rifkin 2012).

It is generally accepted that phenotypic diversity within a population or species is produced by differences in alleles and differences in environmental inputs that modify gene expression (Falconer and Mackay 1996; Jaenisch and Bird 2003; Nanjundiah 2003; Hallgrímsson and Hall 2005;

Keywords. Clonal organisms; development; ecology; epigenetics; evolution; genotype-to-phenotype mapping; individuality; infectivity and resistance; phenotypic variation; stochasticity

Published online: 28 February 2015

Charlesworth and Charlesworth 2010). According to this standard concept, genetically identical organisms kept in the same narrowly controlled environment should be phenotypically identical, which is, however, not the case at all (Gärtner 1990; Veitia 2005; Peaston and Whitelaw 2006; Vogt *et al.* 2008). In practically all cases investigated, there was a residual variation aside of genetic and environmental variation, sometimes exceeding half of the total phenotypic variation (Falconer and Mackay 1996).

The idea of the existence of a third source of phenotypic variation, which is based on developmental stochasticity, is more than a century old (Warren 1902). However, in contrast to genetic variation and environmental variation, stochastic developmental variation (SDV) was mostly regarded as an insignificant background phenomenon resulting from the imperfection of biological processes (Charlesworth and Charlesworth 2010). Authors who recognized its biological relevance often treated it together with the environmental proportion of phenotypic variation on a common conceptual footing under the term phenotypic plasticity *sensu lato* (Nanjundiah 2003; West-Eberhard 2003). SDV can be best determined in laboratory experiments with clonal organisms, in which genetic variation and environmental variation can be kept close to zero. This article uses only such data with the exception of some information on highly variable traits in human monozygotic twins that are produced in the relatively homogeneous environment of the uterus.

This review is an attempt to conceptualize SDV across the entire spectrum of organisms and to elaborate its biological relevance. Special emphasis is given to animals, the most complex organisms with the widest spectrum of SDV generators. The article starts with the definition of some key terms and continues with a historical account of research on SDV to demonstrate its long tradition. It then surveys SDV in major clades of organisms to examine its distribution across the tree of life. Thereafter, a detailed phenomenology of SDV is presented using the animals as an exemplary higher taxon. The following sections deal with the sources and limitations of SDV, its mediation by epigenetic mechanisms, and its implications for genotype-to-phenotype mapping, individuality, applied biology, ecology, and evolution. The last section addresses problems and open questions and makes some suggestions for future research.

2. Definitions

The terms and concepts required to develop the ideas of this article are not consistently used in literature. To avoid misunderstandings, I will here explain how they are applied in the following.

Clonal organisms are at the centre of this work. A clone is an assemblage of individuals genetically identical by descent that originates from asexual reproduction, inbreeding, polyembryony, and artificial cloning (Hughes 1989; De Kroon and van Groenendael 1997; Spratt 2004). Asexual reproduction refers to reproduction without meiosis and fertilization with the offspring being copies of their parent. In animals, it includes budding, fragmentation and apomictic parthenogenesis, in plants vegetative reproduction and apomixis, and in bacteria binary fission, budding, fragmentation and spore formation. Inbreeding is the continued breeding of closely related individuals that finally results in genetic identity. Polyembryony is the development of two or more genetically identical embryos from a fertilized egg. Artificial clones are produced either by embryo splitting or by somatic cell nuclear transfer.

The *genotype* is the genetic make-up of an organism or the entire set of genes it carries (Johannsen 1913). In studies on genotype–phenotype relationships, notably in those with sexually reproducing species, the term is often used in a broader sense characterizing the genetic make-up of a population or even species. Such population genotypes are in fact composed of many different DNA-sequences. In this article, I use the term genotype only in its narrow sense applying to an individual DNA-sequence and its copies. The term *phenotype* refers to the quality or quantity of a trait that can be compared among population members (Mahner and Kary 1997). It mostly refers to distinct morphological, biochemical, physiological, behavioural, or life history traits but can also concern features that characterize specimens as individuals such as physiognomy and coat coloration.

The *phenotypic variation* of a population or species consists of three proportions: genetic variation, environmental variation, and stochastic developmental variation (Falconer and Mackay 1996; Finch and Kirkwood 2000; Nanjundiah 2003). *Genetic variation* comes from changes in the DNA sequence caused by random mutation, transposon shifts, and genetic recombination (Falconer and Mackay 1996). *Environmental variation* is the result of different inputs of the external environment. However, many authors use this term for all sources of non-genetic phenotypic variation, including influences of the internal milieu of organisms. Since the latter is the realm of stochastic developmental variation, I restrict the term *environment* to the external conditions that an organism experiences such as habitat, temperature, water parameters, and food.

In animals, the residual proportion of phenotypic variation that is neither attributable to genetic variation nor environmental variation was called *developmental noise* (Waddington 1957), *intangible variation* (Falconer and Mackay 1996), *third component* (Gärtner 1990), *random noise* (Lewontin 2000), *intrinsic chance variation* (Finch and Kirkwood 2000), or *developmental variation* (Vogt *et al*. 2008). Sometimes, it was also referred to as *developmental instability* (Klingenberg 2003) but this term often includes genetic and environmental variations as well.

Authors working on stochastic processes in unicellular organisms use a variety of different terms, depending on their field of interest or angle of view. Examples are *gene expression noise* (Raj and van Oudenaarden 2008), *cellular noise* (Johnston *et al.* 2012), and *phenotypic noise* (Freed *et al.* 2008). The need for an umbrella term, which unifies all stochastic cellular and developmental processes that contribute to phenotypic variation, prompted me to introduce here the term *stochastic developmental variation* (SDV) in analogy to genetic variation and environmental variation.

The term was first used by Orias and Bradshaw (1992). The word *stochastic* implies a probabilistic nature of the processes involved lacking any predictable order or plan (Meyer and Roeder 2014). *Development* is the progressive change in shape, size, and function during the life of an organism by which its genetic potentials are translated into phenotypes. It covers cleavage, cell differentiation, patterning, and morphogenesis but also tissue regeneration and life history attributes in the adult life. The degree to which the adult life contributes to SDV is dependent on the growth format of an organism, being higher in indeterminately than in determinately growing species.

SDV is often confused with or subsumed under the term *phenotypic plasticity*, which is a hot topic in ecology and evolutionary biology (Pigliucci 2001; Nanjundiah 2003; Fusco and Minelli 2010). In this article, I follow the distinction between the two made by Scheiner (1993): SDV is the production of different phenotypes from a single genotype in a single environment, whereas phenotypic plasticity is the production of different phenotypes from a single genotype in different environments. Both have in common that they are mediated by epigenetic mechanisms (Jaenisch and Bird 2003).

The concept of *epigenetics* was originally introduced by Waddington (1957) to describe the variety of developmental phenomena above the level of the genome in order to link the genotype to the phenotype. Epigenetic mechanisms can be subdivided into molecular and higher-level ones (Hallgrímsson and Hall 2011b). Molecular epigenetics refers to the study of stable alterations in gene expression by mechanisms other than changes in the underlying DNA sequence, for instance, DNA methylation and histone modification (Bird 2002; Lennartsson and Ekwall 2009). Unlike the genetic code, these marks can be erased and rewritten during the lifetime. Higher-level epigenetics includes chemical and mechanical cell-to-cell interactions, self-organization of tissues, and self-reinforcing circuitries including behaviour, metabolism, and neuroendocrine control (Newman and Müller 2005; Vogt *et al.* 2008; Hallgrímsson and Hall 2011b).

3. History of research on SDV

Research on the stochastic developmental proportion of phenotypic variation is almost as old as research on its genetic and environmental proportions. In 1899, Ernest Warren published a short note on the variation of morphometric traits in parthenogenetic broods of the water flea *Daphnia magna* (Warren 1899). Three years later, the same author presented a more detailed work on SDV in parthenogenetic aphis *Longicaudus trirhodus*, in which genetic and environmental variation was minimized by encaging batches on their own leaves (Warren 1902). In the same period of time, Karl Pearson and colleagues collected large amounts of data on the non-genetic and non-environmental variability of repeated traits in individual plants and fungi (Pearson *et al.* 1901). Five years later Raymond Pearl published on the variation of morphometric parameters in communally raised asexual flagellate *Chilomonas paramecium* (Pearl 1906).

Newman and Patterson (1909) were the first to use polyembryonic species for research on SDV. They determined differences in the number of scales in genetically identical quadruplets of nine-banded armadillos. The first discussion of SDV in a textbook also dates from 1909. Wilhelm Ludwig Johannsen argued in his book *Elemente der exakten Erblichkeitslehre* that genetically identical organisms can be phenotypically different even when environmental factors are kept as uniform as possible. He attributed such differences to random events, which may have disturbing or promoting effects on development (Johannsen 1913). Some years later, Sewall Wright used inbred Guinea pig families to analyse genetics of piebald spotting (Wright 1920). He found that variation of colour patterns is determined at about 3% by heredity, 5% by the environment, and 92% by 'developmental irregularities'.

In 1930, Astauroff published a voluminous study on SDV in animals, which covers all aspects of SDV, namely, variation of traits among genetically identical group members raised in the same environment, variation between right and left body sides in bilaterally symmetrical animals, and variation between serially homologous body parts in segmented animals (Astauroff 1930). This paper also includes an extensive list of the earlier literature.

Between the 1930s and 1980s, the number of publications on SDV in animals and plants remained on a relatively low level. Noteworthy are the articles by Wright and Chase (1936), Grüneberg (1954), Reeve and Robertson (1954), Roy (1963), Storrs and Williams (1968), Macagno *et al.* (1973), Gärtner *et al.* (1976), and Spudich and Koshland (1976). Research on right–left differences of traits in bilaterally symmetrical organisms, later called fluctuating asymmetry, developed as a separate field, often interpreting asymmetry as the result of developmental stochasticity but also as the outcome of genetic disturbances and environmental stress (Van Valen 1962; Palmer and Strobeck 1986; Parsons 1992; Leamy and Klingenberg 2005; Graham *et al.* 2010).

SDV in bacteria was first demonstrated in the 1940s. Bigger (1944) reported on the occurrence of cells in clonal

populations of *Staphyllococcus* that could withstand penicillin treatment. These persisters had not acquired antibiotics resistance by mutations and remained sensitive to penicillin after having established a new population. Delbrück (1945) observed broad variation of burst size of viruses from individual *Escherichia coli* cells that could not be accounted for by variation in the size of the bacteria. Benzer (1953) analysed synthesis of β-D-galactosidase in individual *E. coli* and demonstrated heterogeneity of enzyme production among clonal cells under identical conditions. Novick and Weiner (1957) revealed that isogenic *E. coli* can respond to an enzyme-inducing stimulus by an all-or-none response, and Cohn and Horibata (1959) demonstrated that both the formation and non-formation of enzyme could be passed on clonally to the descendants.

Modern research on SDV comes mainly from three directions: stochastic gene expression in unicellular organisms, somaclonal variation in plants, and research on phenotypic diversity in clonal animals kept under highly standardized conditions. Research on stochastic gene expression was initiated by McAdams and Arkin (1997), Thattai and van Oudenaarden (2001), and Elowitz *et al.* (2002), and resulted in hundreds of papers since then, using bacteria and yeast as model organisms. Somaclonal variation, the phenotypic variation of clonal plants raised in tissue culture, was introduced to science by Larkin and Scowcroft (1981). Due to its significance in applied plant biology, this phenomenon has yielded numerous articles as well. However, somaclonal variation is based on genetic and epigenetic mutations (Skirvin *et al.* 1994; Bairu *et al.* 2011; Miguel and Marum 2011), and only the latter aspect is of interest for this review. Research on SDV in animals has been revived by Gärtner's paper on a third component causing random variability beside environment and genotype (Gärtner 1990). Since then, a few dozen articles and book chapters have addressed this topic. In 2012, the *International Journal of Epidemiology* has devoted a special volume to SDV and its potential implications for animals and man (vol. 41, issue 2).

Three important developments in biology boosted research on SDV in the last decade, the invention of new single-cell techniques (Spiller *et al.* 2010; Wang and Bodovitz 2010), the increased application of bioinformatics tools (O'Connor and Mundy 2009; Ning *et al.* 2014), and the progress of molecular epigenetics (Bird 2002; Laird 2010). Single-cell analysis facilitates investigation of non-genetic phenotypic variation in microbial clones, which was lost in earlier bulk measurements. Epigenetics research is expected to contribute significantly to understanding of the mechanisms that mediate SDV, and bioinformatics tools enable processing of huge amounts of genetic and epigenetic data.

In recent years, scientists have realized that SDV has not only disadvantages but also advantages. For instance, Huang (2009) discussed the importance of SDV for cell differentiation and argued that it is 'more than just noise'. Forde (2009) examined the role of SDV in the development of root systems in plants and appraised it 'good noise'. We demonstrated that SDV makes genetically identical animals morphologically and functionally distinct individuals (Vogt *et al.* 2008). Raj and van Oudenaarden (2008) interpreted stochastic gene expression in microorganisms as an important bet-hedging strategy against stress. Nanjundiah (2003) and Eldar and Elowitz (2010) emphasized its possible contribution to the evolution of microbes and multicellular organisms, and Patnaik (2006) pointed at the potential exploitability of SDV for biotechnology. Consideration of these positive biological aspects adds a new dimension to the discussion on SDV and gets it out of the shadows.

4. Occurrence of SDV across the tree of life

In the last chapter, I have cited some examples of SDV from distantly related taxa, which may suggest that SDV is a universal phenomenon. Here, this issue is examined in detail starting with the complex animals and ending with the simple viruses. For reasons of convenience, I use the widespread classification of the living world into Animalia, Plantae, Fungi, Protista, Bacteria, Archaea, and Viruses (Woese *et al.* 1990; Margulis and Schwartz 1997). Protista is a taxonomically abolished assemblage that includes unicellular organisms and some multicellular representatives with low tissue specialization (Adl *et al.* 2012). The viruses are polyphyletic as well and are interpreted either as the most primitive pre-cellular 'organisms' or as a form at the edge of life (Koonin 2012).

Although there are not too many studies on SDV in animals, they cover all major evolutionary lineages. Examples of SDV for morphological, biochemical, physiological, behavioural, and life history traits are available for the Porifera, the most basal branch of the Animalia, the diploblastic Cnidaria, the protostomian Bryozoa, Platyhelminthes, Rotifera, Nematoda, Mollusca, and Arthropoda, and the deuterostomian Ascidiacea and Vertebrata (table 1; figure 1A). In fungi, the closest relatives of the animals, SDV is documented for several species from the two main branches, the Ascomycota and Basidiomycota for gene expression, hyphal morphology and resistance to antimycotics. The species investigated include the model organism *Saccharomyces cerevisiae*, the food contaminant *Aspergillus niger* and the opportunistic pathogen *Cryptococcus neoformans* (table 1; figure 1B).

In plants, the morphologically most diverse organisms aside of animals, information on SDV comes from the morphology of leaves, branches and roots, the colour of flowers, fruits and leaves, some life history traits, and molecular parameters such as gene expression and epigenetic profiles

Table 1. Examples of SDV from different kingdoms of life

Group	Species	Traits investigated	Reference
Animalia			
Rodentia	*Rattus norvegicus* (I)	Broad spectrum of traits	Gärtner *et al.* 1976
Artiodactyla	*Sus scrofa domestica* (C)	Broad spectrum of traits	Archer *et al.* 2003a, b
Carnivora	*Felis silvestris catus* (C)	Coat coloration	Shin *et al.* 2002
Cingulata	*Dasypus novemcinctus* (P)	Broad spectrum of traits	Storrs and Williams 1968
Osteichthyes	*Kryptolebias marmoratus* (S)	Behaviour, gill morphology	Turko *et al*. 2011
Ascidiacea	*Botryllus schlosseri* (A)	Egg production	Stewart-Savage *et al.* 1999
Decapoda	*Procambarus fallax f. virginalis* (AP)	Broad spectrum of traits	Vogt *et al*. 2008
Cladocera	*Daphnia magna* (AP)	Size, age, reproductive traits	Pietrzak 2011
Branchiopoda	*Artemia parthenogenetica* (AP)	Reproductive traits, life span	Browne *et al.* 2002
Diptera	*Drosophila melanogaster* (I)	Asymmetry of bristles	Indrasamy *et al.* 2000
Hemiptera	*Longicaudus trirhodus* (AP)	Morphology, life history traits	Warren 1902
Gastropoda	*Melanoides tuberculata* (AP)	Speed of development	Ben-Ami and Hodgson 2005
Nematoda	*Caenorhabditis elegans* (S)	Life span, locomotion	Herndon *et al.* 2002
Rotifera	*Brachionus calyciflorus* (AP)	Reproductive traits	Gilbert and Schröder 2007
Platyhelminthes	*Maritrema novaezealandensis* (A)	Morphology, behaviour	Koehler *et al.* 2011
Bryozoa	*Electra pilosa* (A)	Morphometric traits	Hageman *et al.* 1999
Cnidaria	*Hydrallmania falcata* (A)	Morphometric traits	Ponczek and Blackstone 2001
Porifera	*Tethya wilhelma* (A)	Patterning of buds	Hammel *et al.* 2009
Fungi			
Saccharomycetes	*Saccharomyces cerevisiae* (A)	Gene expression	Li *et al.* 2010
Eurotiomycetes	*Aspergillus niger* (A)	Variation of mycelium	Vinck *et al.* 2005
Tremellomycetes	*Cryptococcus neoformans* (A)	Resistance to antibiotics	Avery 2006
Plantae			
Asparagales	*Ledebouria graminifolia* (T)	Morphology, life history traits	Shushu *et al.* 2009
Zingiberales	*Musa acuminata* (T)	Pigmentation of leafs and fruits	Sahijram *et al.* 2003
Brassicales	*Arabidopsis thaliana* (T)	Root system	Forde 2009
Lamiales	*Nyctanthes arbor-tristis* (R)	Morphology of leaves	Roy 1963
Solanales	*Nicotiana tabacum* (R)	Leaf and flower morphology	Sakai and Shimamoto 1965
Ericales	*Rhododendron simsii* (T)	Flower colour in bud sports	De Schepper *et al.* 2003
Fabales	*Retama sphaerocarpa* (R)	Branch morphology	Fungairiño *et al.* 2005
Malvales	*Theobroma cacao* (T)	Epigenetic profiles	Rodríguez López *et al.* 2010
Malpighiales	*Populus tremuloides* (A)	Biochemical leaf traits	Smith *et al.* 2011
Protista			
Choanoflagellata	*Salpingoeca rosetta* (A)	Size and morphology of cells	Dayel *et al.* 2011
Mesomycetozoa	*Psorospermium haeckeli* (A)	Size and shape of spores	Vogt and Rug 1999
Amoebozoa	*Dictyostelium discoideum* (A)	Cell fate, spore formation	Nanjundiah and Bhogle 1995
Cryptophyta	*Chilomonas paramecium* (A)	Length and width of cells	Pearl 1906
Ciliophora	*Tetrahymena thermophila* (I)	rDNA expression	Orias and Bradshaw 1992
Apicomplexa	*Plasmodium falciparum* (A)	Expression of surface antigens	Avery 2006
Euglenozoa	*Trypanosoma brucei* (A)	Expression of surface antigens	Figueiredo *et al*. 2009
Chlorophyta	*Volvox sp.* (A)	Cell differentiation	Shelton *et al.* 2012
Bacteria			
Enterobacteriales	*Escherichia coli* (A)	Protein content, cell growth	Tsuru *et al.* 2009
Bacillales	*Bacillus subtilis* (A)	Gene expression, cell fate	Maamar *et al.* 2007
Pseudomonadales	*Pseudomonas aeruginosa* (A)	Bistability and cytotoxicity	Smits *et al.* 2006
Lactobacillales	*Streptococcus pneumoniae* (A)	Development of competence	Smits *et al.* 2006

Table 1 (continued)

Group	Species	Traits investigated	Reference
Actinomycetales	*Mycobacterium tuberculosis* (A)	Resistance to antibiotics	Avery 2006
Archaea			
Sulfolobales	*Sulfolobus acidocaldarius* (A)	Motility	Lewus and Ford 1999
Methanococcales	*Methanococcus jannaschii* (A)	Cell size, DNA content	Malandrin *et al.* 1999
Halobacteriales	*Halobacterium halobium* (A)	Swimming behaviour	Schimz and Hildebrand 1992
Viruses			
Siphoviridae	phage-λ	Lysis and lysogeny	Singh and Weinberger 2009
Baculoviridae	*Gilpinia hercyniae* NPV	Length of virion rods	Ackermann and Smirnoff 1983

A, asexual reproduction; AP, apomictic parthenogenesis; C, artificial cloning; I, inbreeding; NPV, nuclearpolyhedrovirus; P, polyembryony; R, comparison of repeated organs; S, self-fertilization; T, cloning by tissue culture.

(table 1; figure 1C). In table 1, I have listed examples for the monocotyledonous orders Asparagales and Zingiberales, and the dicotyledonous orders Brassicales, Lamiales, Solanales, Ericales, Fabales, Malvales, and Malpighiales. Included is also *Arabidopsis thaliana*, the most widely used model organism in plant biology.

In protists, data on SDV are published for morphometric parameters, cell fate determination, spore formation, and surface antigen expression in species from distantly related clades like Choanoflagellata, Mesomycetozoa, Amoebozoa, Cryptophyta, Ciliophora, Apicomplexa, Euglenozoa, and Chlorophyta (table 1; figure 1D). These examples include

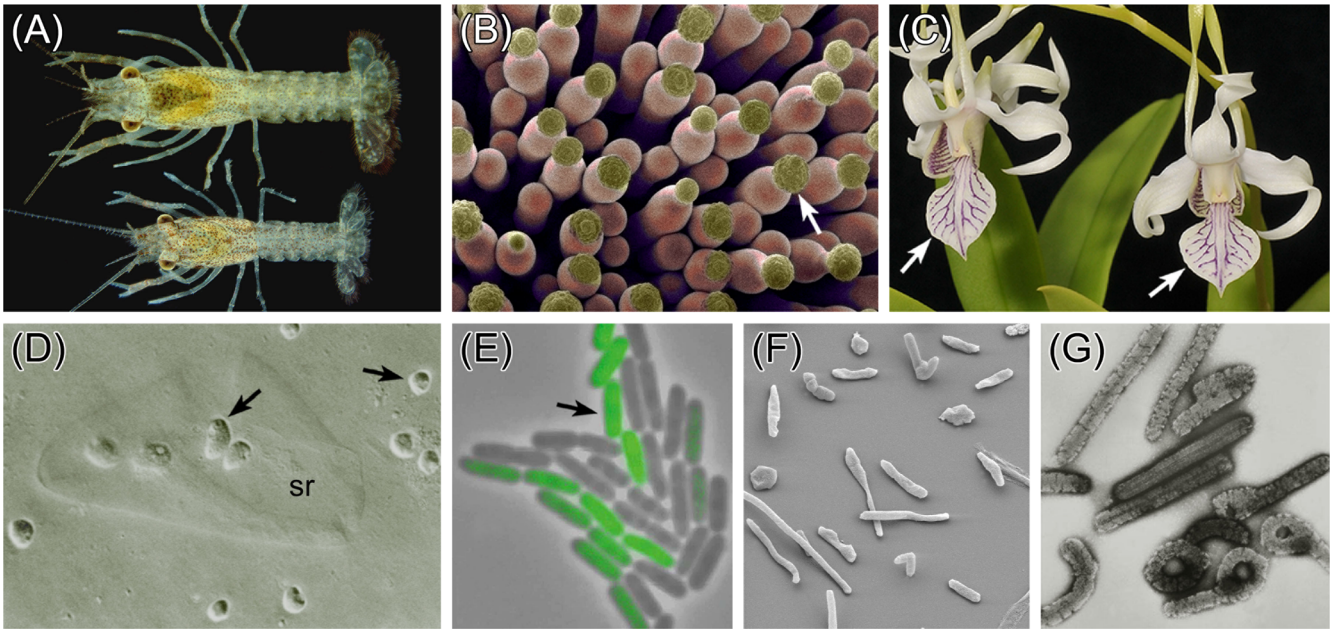

Figure 1. Examples of SDV from all kingdoms of life. (**A**) Variation of size in identically reared batchmates of apomictic parthenogenetic crayfish *Procambarus fallax f. virginalis* (from Vogt *et al.* 2008). (**B**) Variation in asexual formation of conidia (arrow) in fungus *Aspergillus niger* (from Dijksterhuis and Wösten 2013). (**C**) Variation of coloration in iterative flowers of orchid *Dendrobium antennatum*. The colour patterns of the labellum vary between flowers and between right and left sides in each flower (arrows) (photo: Rogier R van Vugt). (**D**) Variation of size and morphology of asexually produced amoebospores (arrows) released from the same spore receptacle (sr) in the protist *Psorospermium haeckeli* (from Vogt and Rug 1999). (**E**) Differential gene expression in bacterium *Salmonella* ser. Typhimurium indicated by green fluorescence protein (arrow). The cells were cultured from a single cell over six generations (from Ackermann 2013). (**F**) Variation of form and size in archaean *Haloterrigena turkmenica* (from Saunders *et al.* 2010). (**G**) Variation of form and length in Marburg virus (photo: Erskine L Palmer and Russell Regnery).

the free-living and colony-forming *Salpingoeca rosetta*, the malaria causing parasite *Plasmodium falciparum,* and the slime mould *Dictyostelium discoideum*, a popular model for cellular differentiation.

There is also sound evidence of SDV in bacteria from different orders concerning growth, gene expression, protein content, behaviour, virulence, and resistance to antibiotics (table 1; figure 1E). Examples are the model organisms *Escherichia coli* and *Bacillus subtilis*, the ubiquist *Pseudomonas aeruginosa*, and the pathogens *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*. In the Archaea, there are examples on SDV for cell size, DNA content, and swimming behaviour in species from different orders (table 1; figure 1F). SDV has even been found in phage-λ and HIV viruses with respect to lysis–lysogeny switching and in rod-shaped baculoviruses and filiform Marburg virus with respect to form and length (table 1; figure 1G).

The occurrence of SDV in all kingdoms of life and all subclades and life forms investigated suggests that it is a universal biological phenomenon inherent in all living beings.

5. Phenomenology of SDV on the example of animals

This section examines the dimensions of SDV, using animals, the evolutionary lineage with the highest complexity of body plans, life styles, and behaviours, as an example. The focus is set on morphological, physiological, behavioural, and life history traits. SDV of qualitative traits is illustrated by photographs and SDV of quantitative traits by the coefficient of variation (CV). CV is the ratio of standard deviation to mean and allows comparison among data sets and species. Information on the phenomenology of SDV in plants is found in Roy (1963), Freeman *et al.* (1993) and Miguel and Marum (2011). Respective data for yeast, protists and bacteria were compiled by Raser and O'Shea (2005), Avery (2006), and Raj and van Oudenaarden (2008).

5.1 *Animal models of SDV*

The outcome of research and the resulting philosophy in a scientific discipline is much dependent on the features of the research models used. Therefore, I want to discuss here briefly the advantages and disadvantages of the common animal models of SDV. These are a dozen vertebrates and invertebrates, which differ in the way they produce genetically identical offspring, the degree to which their housing can be standardized, the quality and quantity of analysable traits, their life history features, and knowledge on genetics and epigenetics.

Common animal models of SDV are inbred strains of mouse *Mus musculus*, rat *Rattus norvegicus*, guinea pig *Cavia porcellus* and fruit fly *Drosophila melanogaster*, the selfing nematode *Caenorhabditis elegans*, polyembryonic nine-banded armadillo *Dasypus novemcinctus*, artificially produced clones of cattle *Bos taurus* and pig *Sus scrofa domestica*, and parthenogenetic lineages of pea aphid *Acyrthosiphon pisum* and water flea *Daphnia pulex*. Several of these species like mouse, rat, and fruit fly are long established as research models (Beck *et al.* 2000; Rubin and Lewis 2000) and manuals for their standardized housing and breeding are available.

Inbreeding, polyembryony, parthenogenesis, and artificial cloning are all suitable means to produce genetically identical research material but the outcome differs in detail (Bailey 1982; Hiendleder 2007; Avise 2008). Inbred lineages of sexually reproducing species are almost 100% genetically identical after more than 40 generations of full-sibling mating. They are homozygous for all autosomal loci and include males and females. In hermaphrodites, prolonged self-fertilization also results in near genetic identity. Monozygous twins and polyembryonic littermates differ from inbred lineages in as far as they are genetically identical among each other but different from their parents. Moreover, they are all of the same sex, either male or female. Artificially manufactured clonemates are genetically identical when embryo splitting is applied but usually differ in mitochondrial DNA when produced by somatic cell nuclear transfer. In obligate apomictic parthenogenetic lineages, all members are genetically identical females.

Experiments on SDV also require maximum standardization of the environmental parameters. This is easier achieved with small animals like fruit flies, water fleas, and aphids than with large animals like pigs and cattle. The small-sized models have the additional advantage of cheaper mass culture and a much shorter generation time. However, they are unsuitable for individual biochemical and physiological measurements and individual analyses of transcriptome, proteome, and methylome. Mouse and rats have appropriate sizes for both, mass culture under highly standardized conditions and individual biochemical analyses.

The common SDV models also show considerable differences in the quality and quantity of analysable characters. For instance, variation in coloration and spotting is the rule in some guinea pig and cattle lineages but is rare or absent in the other species. Armadillos, insects, and water fleas possess rigid external structures such as scales and sensory setae that allow exact measurement and counting. *Caenorhabditis elegans*, in contrast, has very few morphological traits suitable for measurement. The life history features vary broadly as well. For instance, *Caenorhabditis elegans* has a generation time of 3–4 days and a life span of 2–3 weeks, which is in sharp contrast to cattle that has generation times of 2 years and average life spans of 15 years. The number of offspring per clutch is usually 1 in cattle, 3–8 in mouse and up to 30 in water flea.

There are also considerable differences with respect to development and growth format. The mammals and daphnids develop directly, whereas insects and the nematode develop indirectly through larval stages. *Caenorhabditis elegans* is exceptional because it has a constant cell number and an invariant cell fate pattern. The insect and mammalian models show determinate growth, i.e. they stop growth at the beginning of the reproductive life period, whereas daphnids grow indeterminately and change morphological traits until the end of life. The early life stages of the mammalian species are not directly observable because they develop in the uterus, whereas in the invertebrate models all life stages are accessible for observation, sampling, and manipulation.

Knowledge on genetics is quite good in most of the models. Mouse, rat, guinea pig, and fruit fly are already used for more than a century to study genetic issues (Rubin and Lewis 2000; Paigen 2003). Whole genome sequences are available for mouse, rat, cattle, pig, guinea pig, nine-banded armadillo, fruit fly, nematode, pea aphid, and water flea. Methylation of the DNA, which seems to be a prime epigenetic mediator of SDV, is intensely investigated in the mammalian models and less intensely in aphids and daphnids (Walsh *et al.* 2010; Chen and Riggs 2011). In *Drosophila* and *Caenorhabditis* the DNA is unmethylated (Raddatz *et al.* 2013).

A few years ago, I introduced the obligate parthenogenetic marbled crayfish *Procambarus fallax f. virginalis* (figures 1A and 4D) as a new model for research on SDV (Vogt 2008; Vogt *et al.* 2008). This crustacean meets very well the requirements for studying SDV in the laboratory, namely, genetic identity of all population members, housing in simple environments, and possession of numerous characters easy to analyse. It has an adult size of 4–12 cm, a generation time of about 6 months and a life span of 2–3 years. Marbled crayfish are indeterminately growing and can reproduce about seven times in their life having up to 400 siblings per clutch. The eggs, embryos and first three juvenile stages are brooded on the maternal pleopods (figure 4D). All life stages can be raised individually or communally in very simple laboratory settings and can be fed with a single pellet food (Tetra WaferMix) throughout life, enabling maximum standardization of the environmental conditions (Vogt 2008, 2011). The genome is already fully sequenced and a first draft of the genome assembly is available. The DNA is methylated in all life stages having a methylation level close to that of the mammalian models (Vogt *et al.* 2008, 2013).

5.2 *Inter-individual SDV*

This section gives an overview of the dimensions of SDV in genetically identical groups of animals raised under strictly controlled laboratory conditions. Included is also some information on highly variable traits in human monozygotic twins that arise during embryonic development. Most articles on inter-individual SDV in animals include information on only one or two traits. Broader spectra of traits, which allow the identification of differences between traits and trait categories, were analysed by Gärtner and colleagues, who investigated 25 quantitative traits in 58 inbred groups of rats each consisting of 20 specimens (Gärtner *et al.* 1976; Gärtner 1985, 1990). Likewise, Tordoff and colleagues examined nine biochemical and behavioural traits in 40 inbred groups of mice (Reed *et al.* 2007; Tordoff *et al.* 2007a, b). Storrs and Williams (1968) studied 20 morphological and biochemical traits in 16 armadillo quadruplets, and Friend and colleagues investigated 24 morphological, biochemical, and behavioural characters in two groups of cloned pigs (Archer *et al.* 2003a, b). We investigated 22 morphological, biochemical, behavioural, and life history traits in 28 batches of the parthenogenetic marbled crayfish (Vogt 2007, 2010; Vogt *et al.* 2008, 2009).

5.2.1 *Morphological traits:* The variation of qualitative morphological characters among identically reared isogenic animals is often seen at first glance. Examples are the horn form in cloned cattle (figure 2A), the hairiness in cloned pigs (figure 2B), and the arrangement of scales in the head shields of polyembryonic armadillo littermates (figure 2C). SDV can be extremely broad in some traits, for example, in fingerprints (figure 3A), palm prints, irises, and retinas of humans (Daugman and Downing 2001; Jain *et al.* 2002; Kong *et al.* 2006), and in noseprints of cattle (figure 3B) (Yang *et al.* 2012). These traits become diverse in the relatively uniform environment of the uterus and persist largely unchanged throughout life. In contrast to the DNA profiles, these traits differ among clonemates and are therefore used for individual authentication of humans and cattle.

Coat coloration is another qualitative trait that can vary widely between identically raised clone members. For instance, inbred A^{vy} mice show coat colours from pure yellow to agouti (figure 4A), and parthenogenetically produced batchmates of pea aphid show whitish to green coloration (figure 5A). Much more variable than the colour hue is colour patterning as shown for inbred guinea pigs (Chase 1939), cloned Holstein cattle (figure 4B), cloned cats (figure 4C), and parthenogenetic marbled crayfish (figure 4D). The marmoration motifs of the latter differ greatly between mother and offspring and among batchmates (figure 4D). Each of the many hundred specimens examined by us had a unique marmoration pattern that unambiguously identified the individuals, despite their genetic identity (Vogt *et al.* 2008).

SDV of metric (measurable) and meristic (countable) morphological traits is mostly relatively small (table 2). For example, the CVs of body length in two clones of red-spotted cherry salmon *Oncorhynchus masou macrostomus*

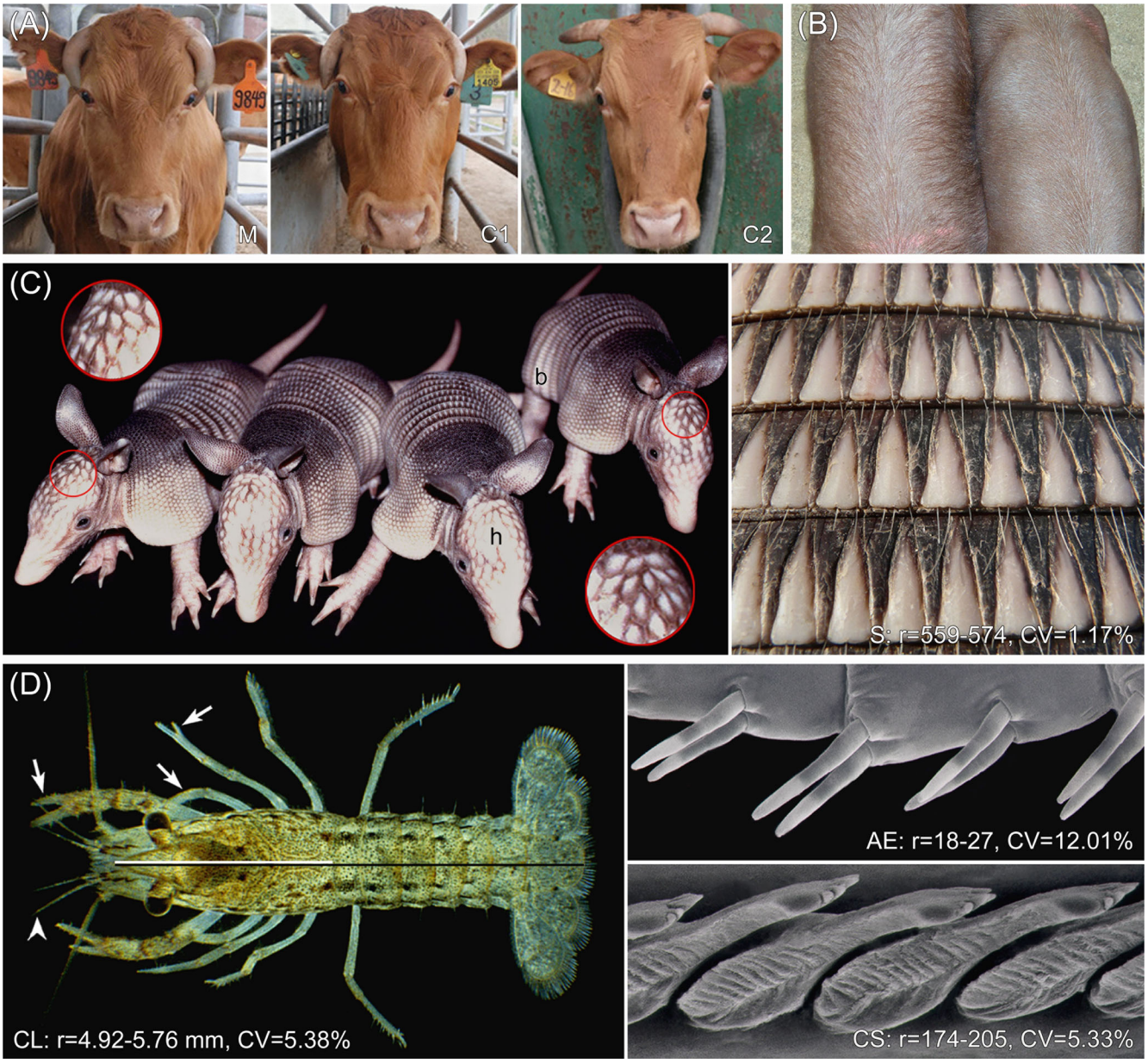

Figure 2. SDV of morphological traits in animals. (**A**) Variation of horn pattern in cloned Hanwoo cattle. Clone 1 (C1) has a horn similar to the nuclear donor mother (M) but different to its clonemate (C2) (from Yang *et al.* 2012). (**B**) Variation of hair pattern in cloned Duroc pigs. The left specimen has longer and sparser hair than its clonemate on the right (from Archer *et al.* 2003a). (**C**) Differences in patterns of skeleton shields in a quadruplet of polyembryonic nine-banded armadillo. Red circles show variation in head shields (h) of two littermates. The banded shield (b) is particularly suitable for analysis of SDV due to highly regular arrangement of scales as shown in the right panel. Inscription gives range (r) and coefficient of variation (CV) of the number of scales (S) in the banded shields of one quadruplet (left photo: Brian Bagatto; right photo: David G. Haskell; data from Newman 1913). (**D**) Variation of metric and meristic traits in marbled crayfish. Analysed were carapace length (white bar), total length (black bar), number of aesthetascs on 1st antennae (arrowhead) and number of corrugated setae on pereopods 1 to 3 (arrows). Left panels show scanning electron micrographs of aesthetascs and corrugated setae. Inscriptions give ranges and CVs of carapace length (CL), total number of aesthetascs (AE) and total number of corrugated setae (CS) for a batch of 11 stage-6 juveniles (from Vogt *et al.* 2008).

were 4.65% (n=24) and 5.00% (n=22) (Iguchi *et al.* 2001). The CVs of the number of scales in the banded region of polyembryonic armadillos (figure 2C) were even smaller varying only between 0.39% and 3% in 16 quadruplets

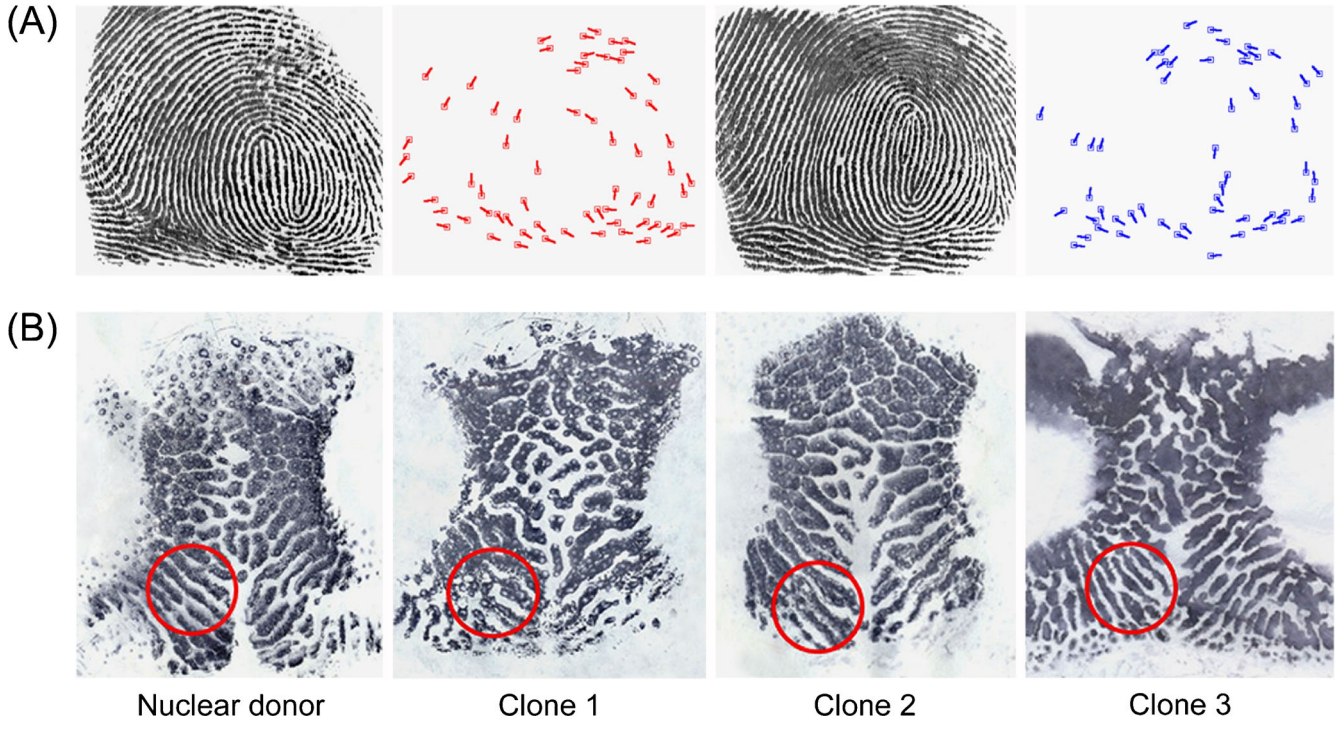

Figure 3. Examples of particularly variable morphological traits. (**A**) Fingerprints of corresponding index fingers of human monozygotic twins showing differences in pattern of ridges (left panels). The differences become particularly obvious in the minutiae patterns (right panels) extracted from the fingerprints for automatic authentication (from Jain *et al.* 2002). (**B**) Noseprints of cloned Hanwoo cattle showing striking differences between nuclear donor cow and clonemates 1 to 3 in comparable areas (red circles) (from Yang *et al.* 2012).

(Storrs and Williams 1968). In batches of marbled crayfish juveniles, the CVs of carapace length, total length, and the numbers of olfactory and gustatory sense organs (figure 2D) varied between 2.73% and 18.57% but were mostly below 10% (Vogt *et al.* 2008; unpublished data).

Interestingly, in a given group of animals CVs for different morphological traits were usually not the same. For example, in a newborn armadillo quadruplet, CVs of the weights of brain, heart, and spleen were 5.52%, 14.65%, and 29.99%, respectively (table 2). Likewise, in 12 juvenile stage-3 batchmates of marbled crayfish CVs of carapace length, number of olfactory aesthetascs, and number of gustatory corrugated setae were 2.73%, 6.43%, and 3.72% (table 2).

5.2.2 *Biochemical and physiological traits:* SDVs of biochemical traits can either be small or high depending on trait and species. For example, the blood parameters serum protein, glucose and albumin in cloned pigs had CVs below 10% (table 2). Blood calcium, which is generally narrowly regulated, had a CV below 1%. In contrast, water content, fat content and ash had CVs between 10% and 20% in inbred mice (Dawson 1970). Higher CVs of 20% to 135% were determined for the hormones cortisol, growth hormone, triiodothyronine, thyroxine, insulin, and adrenalin in polyembryonic armadillos and cloned pigs and goats (table 2).

Growth differences among identically raised clonemates are often obvious at first glance as shown for parthenogenetic marbled crayfish (figure 1A), parthenogenetic pea aphids (figure 5A), and cloned pigs (figure 5B). Quantitatively, growth differences can be determined by comparison of size and weight at a given time, size and weight increment in a given period of time, and, in arthropods, the proportion of different instars at a given time. Examples of CVs of body weight are 5.72% in a newborn armadillo quadruplet and 30.91% in a group of 8 batchmates of marbled crayfish at day 152 of life (table 2). In male groups (n=10) of inbred mice from 40 strains, the CVs of daily weight gain varied between 0 and 200% (mean: 19.61%) (Tordoff *et al.* 2007a).

Considerable variation in growth was also noted when batchmates of marbled crayfish were individually raised in a 12-well microplate through the late embryonic and early juvenile stages (figure 5C). In the lecithotrophic embryos and juvenile stages 1 and 2, development was rather uniform, but from juvenile stage 3, the first feeding stage, the speed of development became increasingly diverse. An

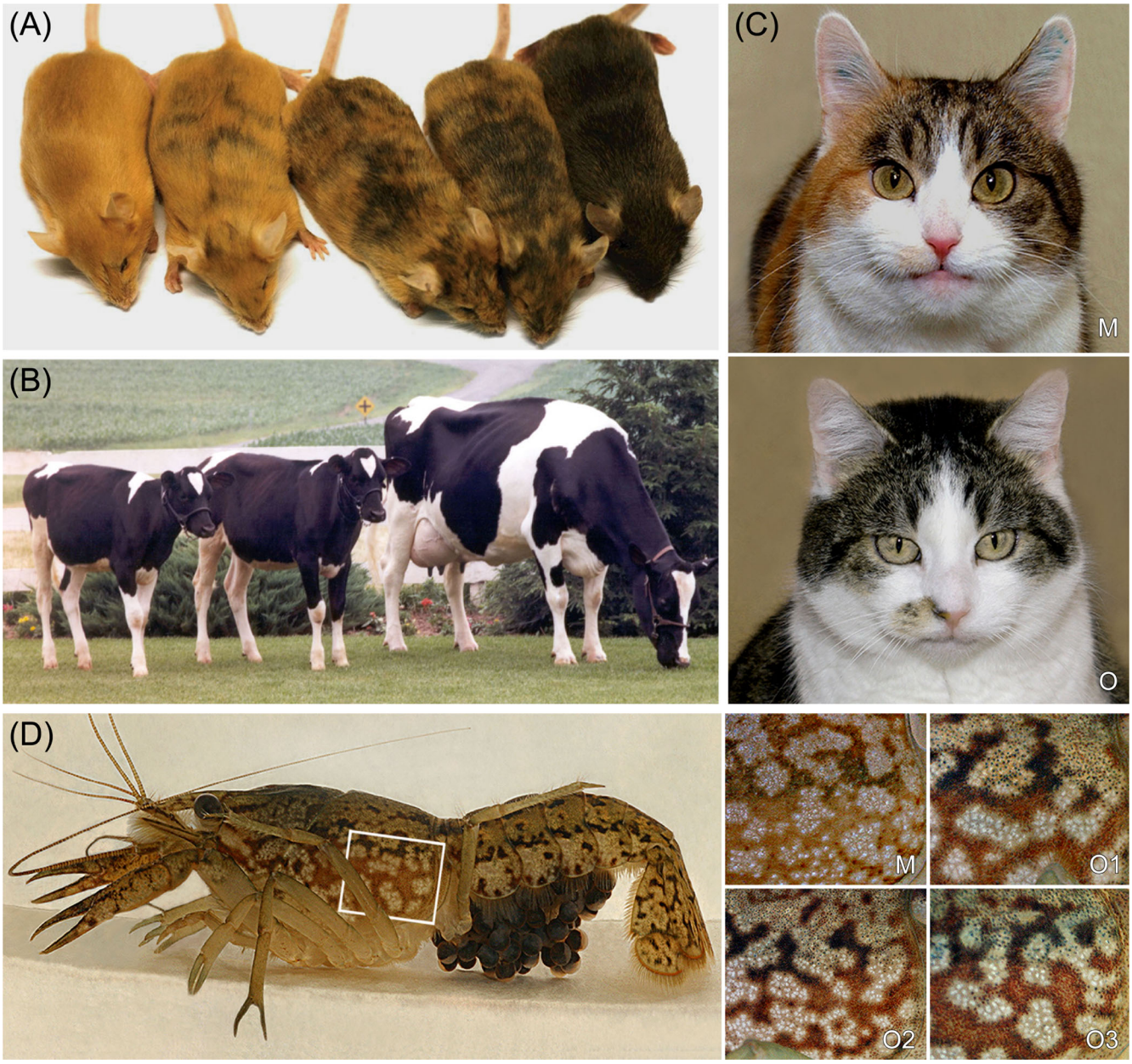

Figure 4. SDV of coloration in animals. (**A**) Inbred A^{vy} mouse littermates showing colour variation from pure yellow (left) to pseudoaguti (right) (from Cropley *et al.* 2010). (**B**) Monozygotic twins of Holstein cattle derived from a split embryo and their donor mother showing differences in spotting pattern (from Seidel *et al.* 2003; photo: John F. Hasler). (**C**) Nuclear donor mother (M) and cloned offspring (O) of cat showing marked differences in both colours and spotting patterns (from Shin *et al.* 2002; photos: Larry Wadsworth). (**D**) Parthenogenetic marbled crayfish showing variation in marmoration patterns. White frame indicates posteriolateral part of cephalothorax used for comparison of colour patterns. The four panels on the right show striking differences between a mother (M) and three adult offspring (O1–O3) of the same batch (from Vogt *et al.* 2008).

increase of SDV of growth with age was also observed in a group of 8 marbled crayfish, which had CVs of body weight of 10.29%, 14.37%, 20.98%, 30.91%, and 48.05% at days 71, 101, 143, 152, and 351 after hatching, respectively.

The semi-independency of traits with respect to SDV as observed for morphological characters is also typical for biochemical and physiological traits. To give an example, in a group of five clonemates of pig, the CVs for serum protein, blood urinary nitrogen and cortisol were 3.73%,

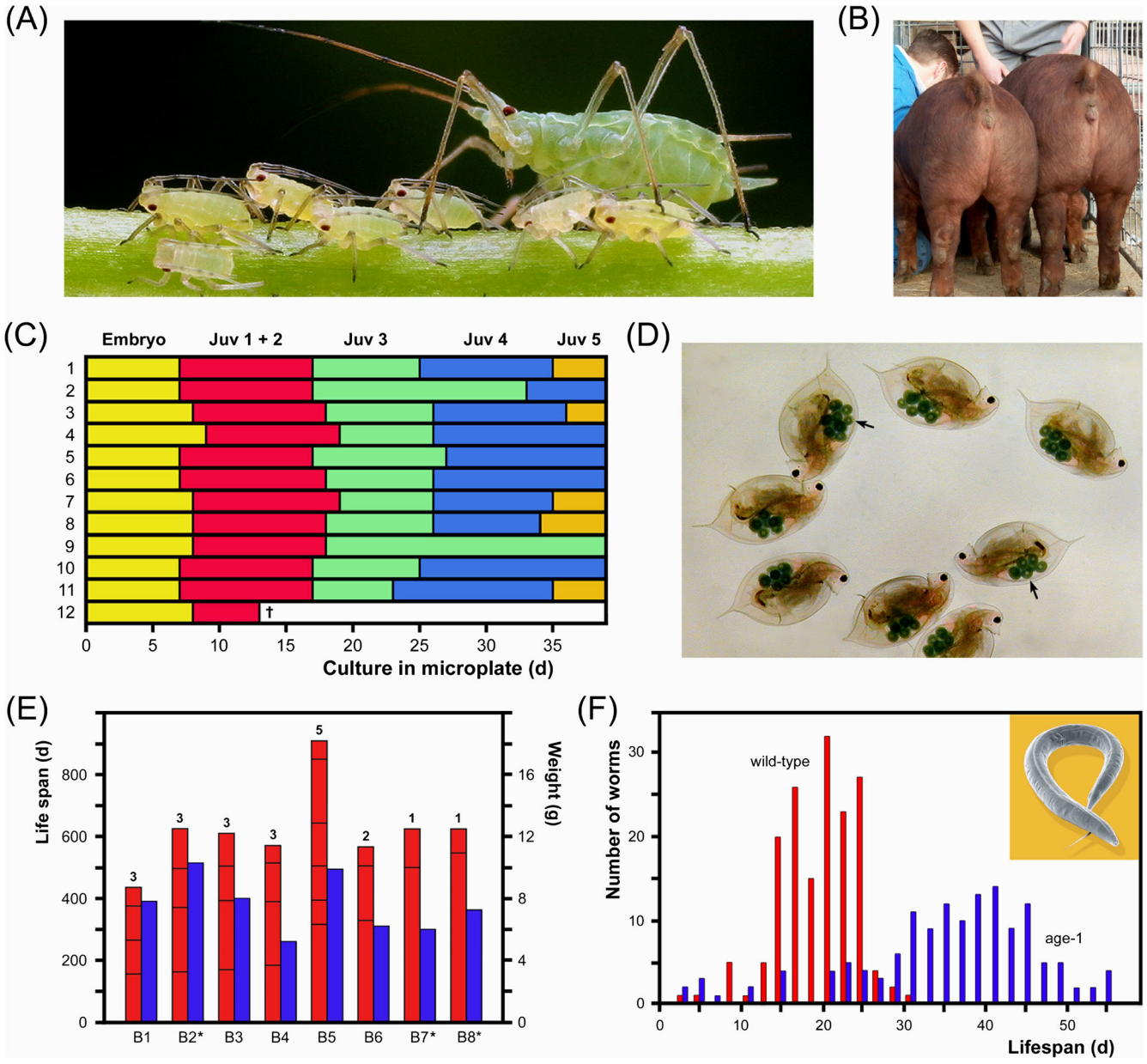

Figure 5. SDV of life history traits in animals. (**A**) Differences in coloration and size among parthenogenetically produced offspring of pea aphid (photo: Alex Wild). (**B**) Size differences between 27-weeks old cloned Duroc pigs originating from the same nuclear donor cell line and born to the same recipient mother. The pigs were kept communally and had unlimited access to food and water (from Archer *et al.* 2003a). (**C**) Variation in speed of development among 12 batchmates of parthenogenetic marbled crayfish raised individually in the same microplate. Shown is a 39-day period from 80% embryonic development to juvenile stage 5. Differences in development are small in the lecithotrophic period and increase markedly from stage 3, the first feeding stage (from Vogt *et al.* 2008). (**D**) Variation in body size and egg number (arrows) in highly synchronized parthenogenetic water fleas (photo: Winfried Lampert). (**E**) Variation of life span, body weight and reproduction frequency in eight communally reared batchmates of marbled crayfish (B1–B8). Life span is indicated by red columns, final weight by blue columns, frequency of reproduction by figures on red columns, and time points of egg laying by horizontal bars in red columns. Specimens indicated by asterisks were sacrificed for biochemical analysis; the other crayfish died a natural death (from Vogt 2015). (**F**) Variation of life span in wild-type (red) and long-lived age-1 (blue) strains of selfing nematode *Caenorhabditis elegans* (redrawn after Kirkwood and Finch 2002; photo: Jürgen Berger).

Table 2. Examples of SDV in identically reared groups of isogenic animals

Species	Trait	Range/mean[1]	CV (%)	Reference
Rattus norvegicus (I), n=18	Mandible length	26.8 mm	1.49	Flamme 1977
	Body weight	333 g	12.91	
	Heart weight	0.87 g	10.34	
	Liver weight	11.24 g	11.12	
	Serum protein	67.3 g/L	9.66	
	GOT	43.3 U/L	36.72	
Dasypus novemcinctus (P), n=4	No. of scutes in BR	526-531	0.39	Storrs and Williams 1968
	Body weight	52.61-60.30 kg	5.72	
	Brain weight	5.23-5.86% BW	5.52	
	Heart weight	0.45-0.64% BW	14.65	
	Spleen weight	0.13-0.24% BW	29.99	
	Glutamate in brain	12.24-20.57 rl	21.06	
	Alanine in brain	3.33-12.29 rl	55.80	
	Adrenaline in AG	0.05-1.60 µg/g	102.41	
Sus scrofa domestica (C), n=5	Weight at 27 wk	81.6-102.1 kg	9.25	Archer *et al.* 2003a
	Serum protein	7.0-7.7 g/dL	3.73	
	Blood calcium	10.7-10.9 mg/dL	0.93	
	Blood albumin	3.6-4.3 g/dL	7.25	
	Blood glucose	70-88 mg/dL	9.20	
	Cortisol	3.2-6.7 µg/dL	28.98	
	Triiodothyronine	43.41-54.63 ng/dL	20.54	
	Blood urinary nitrogen	8.9-11.6 mg/dL	14.04	
Capra aegagrus hircus (C), n=5	Weight at 52 wk PW	43.8 kg	15.34	Landry *et al.* 2005
	Growth hormone	3.4 ng/mL	135.29	
	Insulin-like GF 1	177.9 ng/mL	44.74	
	Thyroxine	4.3 µg/dL	27.91	
	Insulin	17.7 µIU/mL	66.67	
Oncorhynchus masou macrostomus (C), n=22	Standard length	8.0 cm	5.00	Iguchi *et al.* 2001
	Body weight	8.2 g	12.20	
	Horizontal movement	7.64 grids/min	112.43	
	Hiding	1.08 freq/12 min	215.74	
	Benthic feeding	31.28 freq/12 min	96.23	
Procambarus fallax f. virginalis (AP), adults, n=8	Total length at 152 d	3.4-4.4 cm	10.26	Vogt *et al.* 2008
	Carapace length at 152 d	1.6-2.0 cm	9.55	
	Body weight at 152 d	0.99-2.40 g	30.91	
	Life span	437-910 d	21.31	
	Reproduction cycles	1-5	49.52	
	First spawning	157-531 d	52.46	
	No. of offspring at 430 d	0-219	90.68	
stage-3 juveniles, n=12	Carapace length	3.06-3.36 mm	2.73	
	No. of aesthetascs	10-12	6.43	
	No. of corrugated setae	94-106	3.72	

All groups were reared in captivity in highly standardized environments. [1] means are given when data on ranges were not available. AG, adrenal gland; AP, apomictic parthenogenesis; BR, banded region; BW, body weight; C, artificial cloning; CV, coefficient of variation; freq, frequency; GF, growth factor; GOT, glutamic-oxaloacetic transaminase; I, inbreeding; P, polyembryony; PW, post weaning; rl, relative level.

14.04%, and 28.98%, respectively. This semi-independency may depend on different buffering as explained later or on whether the biochemical trait of interest is based on regulation of the flux through a pathway or regulation of concentrations. Flux regulation may be accompanied by larger variations in the levels of intermediates (Cornish-Bowden and Nanjundiah 2006).

5.2.3 *Life history traits:* Life history traits comprise reproduction, life span, and mortality. They are particularly important because they markedly influence demography and fitness. An example of SDV of reproductive traits is presented in table 2 for 8 batchmates of marbled crayfish reared communally from hatching to death. The time between hatching and first spawning varied from 157 to 531 days, the number of breeding cycles from 1 to 5 and the number of offspring per female at day 430 from 0 to 219, corresponding to CVs of 52.46%, 49.52%, and 90.68%. The allocation of metabolic resources towards reproduction and growth varied broadly in this group as well (figure 5E). Other examples of

SDV of reproductive traits come from batchmates of parthenogenetic water flea, which had different numbers of embryos in their brood chamber at a given time (figure 5D). Under specific laboratory conditions, these crustaceans can produce either normal eggs or differently structured resting eggs, and this feature was explained to about 98% by SDV and only to 2% by environmental heterogeneity (Lajus and Alekseev 2004).

Life span is also quite variable among identically reared clonemates. For instance, in a group of 14 inbred mice this trait varied from 27 to 147 days, and in 16 inbred rats from 16 to 113 days (Williams and Pelton 1966). In the above-mentioned group of 8 marbled crayfish, reproducing specimens reached ages between 437 and 910 days, corresponding to a CV of 21.31% (table 2). It has to be noted that this value does not include life span data of batchmates that had died prior to maturity. Broader spectra of relative life spans ranging from 3 to 30 days and 3 to 55 days were found in two strains of *Caenorhabditis elegans* (figure 5F) in which all group members were considered.

5.2.4 *Behavioural traits:* SDV of behaviour is less well investigated than SDV of morphological, biochemical, and life history traits but there are some interesting examples published for clonal fish and mammals. For example, Archer *et al.* (2003b) quantified food preference, temperament and time budget in cloned pigs and found that intraclonal variation could reach dimensions comparable to variation in naturally bred control groups (figure 6A). Tordoff *et al.* (2007a, b) investigated voluntary uptake of water, sodium and calcium in 40 strains of inbred mice and found considerable variation between and within strains. Iguchi *et al.* (2001) analysed SDV of movement, feeding, alerting and threat behaviour in clonal salmon *Oncorhynchus masou macrostomus* and revealed CVs between 96.23% and 215.74% (table 2), indicating pronounced behavioural individuality. Turko *et al.* (2011) examined voluntary emersion in isogenic strains of self-fertilizing mangrove rivulus *Kryptolebias marmoratus* and found that clonemates spent very different proportions of their time (0-78%) out of water. Interestingly, these behavioural differences were coupled with differences in gill morphology.

There are also some interesting examples of SDV of behaviour in invertebrates. For instance, Schuett *et al.* (2011) recorded different escape responses to predator attack among clonemates of the parthenogenetic pea aphid: dropping off the plant, non-dropping, and inconsistent behaviour. In marbled crayfish, variation of behaviour among batchmates became obvious as soon as the juveniles started to move and feed (Vogt *et al.* 2008). Juveniles are principally able to move from stage 2 on, but under natural conditions, this life stage is firmly hooked onto the maternal pleopods with close contact to each other. When such juveniles were taken from the pleopods and evenly distributed on a net, they first roamed around and then hooked into the net to stay in this position for several days. Of 38 batchmates, 6 preferred to hook in individually, while the other 32 adhered in smaller groups with the individuals keeping antennal contact to each other.

A remarkable divergence of behaviour from the same initial status occurred when stage-6 batchmates of marbled crayfish were placed in groups of five into culture vessels without shelter (Vogt *et al.* 2008). In the following 34 days, social hierarchies were gradually established. At the end of the experiments, each group consisted of 1 dominant, 1–2 subdominants and 2–3 subordinates. During establishment of the hierarchies, the dominants developed increasingly offensive behaviours, whilst their counterparts developed increasingly defensive and avoiding behaviours. Interestingly, growth of the dominants speeded up compared to the subdominants and subordinates (figure 6B) although all specimens had unlimited access to the food and fed regularly as revealed by the externally visible filling of the intestine. These differences in behaviour and growth probably developed from very small behavioural differences via self-reinforcing circuitries involving metabolism and neuroendocrine feedback. Such pronounced differences were not established when shelters were available.

5.3 *Intra-individual SDV*

This section deals with stochastic developmental differences between mirror symmetrical structures of bilaterian animals and serially repeated parts of homonomously segmented animals.

5.3.1 *Phenotypic variation between body sides in bilaterally symmetrical animals:* The right and left body sides of bilaterally symmetrical animals include the same genes and are normally exposed to the same environmental conditions. Therefore, bilaterally paired structures should be identical but this is only rarely the case. The random asymmetry around a zero mean value is called fluctuating asymmetry (FA) (Van Valen 1962; Palmer and Strobeck 1986; Schilthuizen and Gravendeel 2012). FA can be caused by genetic disturbances, environmental stress, developmental stochasticity, or a mixture of them (Parsons 1992; Graham *et al.* 2010). Babbitt (2008) partitioned FA of wing parameters in a monoclonal population of cotton aphid *Aphis gossipyii* raised along a temperature gradient from 12.5°C to 25°C and found that developmental stochasticity was responsible for about 50% of the overall response of FA. In this section I have only considered laboratory studies with isogenic populations in which genetic and environmental stresses should be the same for all group members.

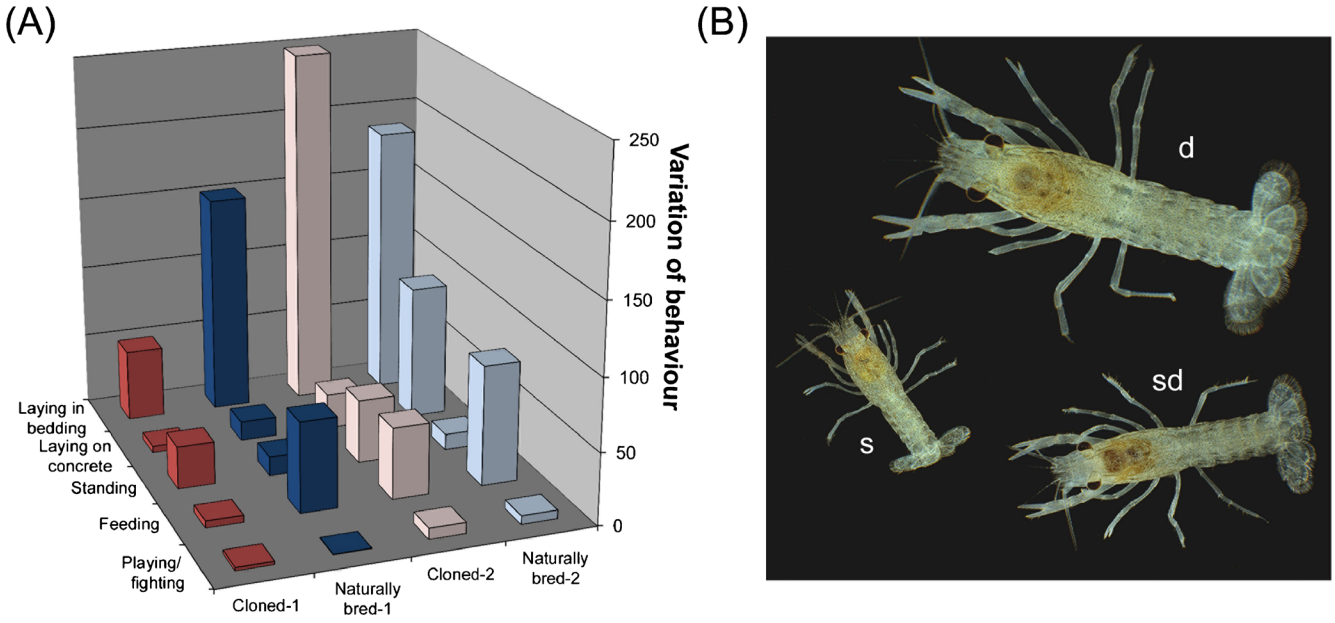

Figure 6. SDV of behavioural traits in animals. (**A**) Variation of time budget in two litters of cloned female pigs from the same fetal cell line in comparison to two naturally bred litters (from Archer *et al.* 2003b). (**B**) Variation of agonistic behaviour and concomitant growth differences in batchmates of marbled crayfish kept for 34 days under conditions of social stress. The experiment was started with five size-matched batchmates of indifferent agonistic behaviour and ended with one dominant (d), two subdominants (sd) and two subordinates (s) of remarkably different size, although food was available in excess and not monopolized (from Vogt *et al.* 2008).

FA data come mainly from external morphological traits such as colour pattern, metric body parameters, or the quantity of setae (figure 7A–C). Internal characters like skeletal elements or blood vessel patterns (figure 7D) were less frequently used. Arthropods are particularly suitable for research on FA because they have a rigid exoskeleton studded with numerous appendages and sensory setae allowing exact measurement and counting. Moreover, in longer-lived indeterminately growing species like marbled crayfish, the shed exuviae provide an excellent archive for individual longitudinal studies.

A particularly high variation between body sides was recorded for colour patterning of the integument in parthenogenetic marbled crayfish (figure 7C), inbred guinea pigs (Chase 1939), and cloned Holstein cattle (Seidel *et al.* 2003). The same holds for sexually reproducing species with spotted or striped colour coats (Murray 2003). High right-to-left differences are also common in fingerprints, irises, and retinal vessels of humans (figure 7D) and in noseprints of cattle (figure 3B) (Markow and Gottesman 1989; Daugman and Downing 2001; Yang *et al.* 2012). These differences are already well established in newborn babies or calves, which have experienced the rather uniform environment of the uterus only.

FAs of metric and meristic morphological traits are usually less prominent. For example, in inbred mice strains, FA of femur length, humerus length, tibia length, and mandible centroid size varied from about 2 to 5% (Leamy *et al.* 2001). Higher FA values were recorded for the number of bristles on the head and thorax of wild type and 10 mutant strains of *Drosophila* (figure 7A). In these lineages, mean FAs of the ocellar, notum, and scutellar bristles varied from 11 to 24%, 0 to 14%, and 0 to 20%, respectively (Indrasamy *et al.* 2000). Interestingly, FAs of the three traits also showed considerable within-strain variation. For example, in mutant strain Ax^{9B2} the ocellar, notum and scutellar bristles had FAs of 20%, 11%, and 4%.

In marbled crayfish, FAs of the numbers of aesthetascs and corrugated setae varied considerably between batches from different mothers and between consecutive juvenile stages of the same batch. They mostly fluctuated between 3% right asymmetric and 3% left asymmetric, having extremes of about 6% (figure 7E). FAs of the two traits were usually not correlated, as shown by the analysis of the offspring of 4 mothers across 5 juvenile stages. Quite often, FAs of both traits even had an opposing symmetry in a given batch. Moreover, FAs shifted with ongoing development from right asymmetric to left asymmetric and vice versa, suggesting that asymmetries may be corrected when they exceed a certain range.

This idea is supported by longitudinal analysis of the exuviae of individuals reared under constant environmental

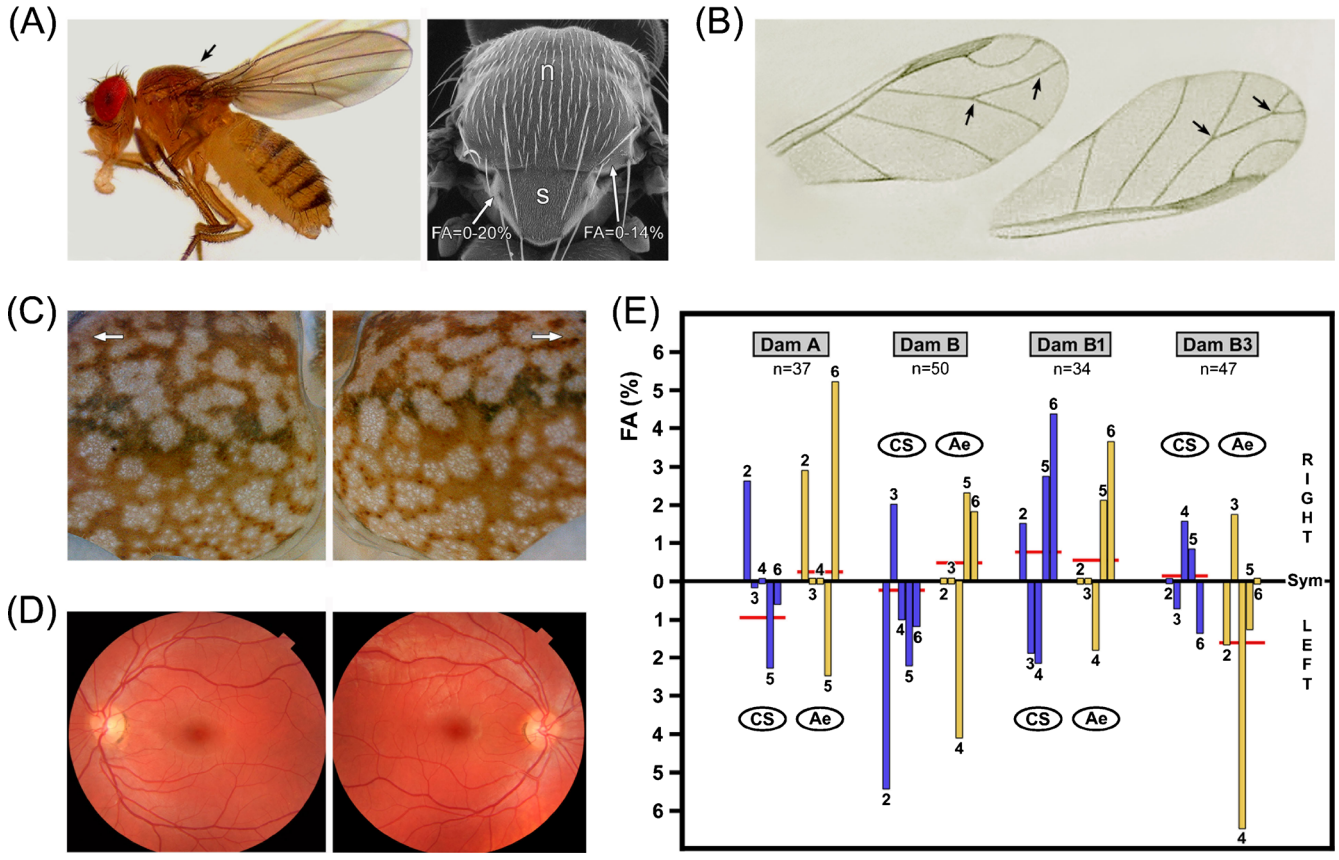

Figure 7. Fluctuating asymmetry (FA) in laboratory reared animals. (**A**) FA in dorsal thoracic bristles of fruit fly. Left panel shows location of bristles in animal (arrow). Right scanning electron micrograph shows bristles in detail and gives ranges of FA for bristles on notum (n) and scutellum (s) in 11 inbred strains (left photo: Pascal Radtke; right photo: Eric C Lai; data from Indrasamy *et al.* 2000). (**B**) Asymmetry of veins (arrows) in right and left wings of cotton aphid (from Babbitt 2008). (**C**) Differences in marmoration pattern between left and right posteriolateral cephalothorax areas of marbled crayfish. Arrows point towards head. (**D**) Differences in retinal blood vessel pattern between right and left eye of young man (photo: Mikael Häggström). (**E**) Variation of FA of meristic traits among batches and juvenile stages of marbled crayfish. The graph includes data on the numbers of aesthetascs (Ae) and corrugated setae (CS) of four batches derived from mothers A, B, B1 and B3. Dams A and B were from different laboratory lineages, and dams B1 and B3 were daughters of dam B. Each batch was analysed from juvenile stage 2, in which the sense organs appear, to juvenile stage 6 (stages indicated by numbers on bars). FA is expressed as percent deviation from perfect symmetry (Sym) to the right or left body side. Red horizontal bars indicate mean of all stages of a batch. Note differences of FA between batches, temporal dynamics within batches, and semi-independent behaviour of traits.

conditions (Vogt *et al.* 2008). For example, in a specimen raised from juvenile stages 6 to 14, FA of the aesthetascs shifted from left asymmetric to symmetric to right asymmetric and back to left asymmetric. A similar but chronologically postponed pattern was observed for the corrugated setae of the 2nd pereopods, whereas the corrugated setae of the 1st pereopods remained right asymmetric all the time. These results corroborate that different traits behave as semi-independent modules, as earlier shown for inter-individual SDV.

Good examples of FA of internal structures aside of vertebrate skeletal elements and teeth are the retinal blood vessels of humans (figure 7D) and the unpaired descending artery of marbled crayfish. This artery originates from the unpaired heart, which is located dorsally in the median plane, runs around the hindgut on either side and terminates ventrally in the subneural artery that is located in the median plane as well. Serial sectioning of 133 identically reared juveniles revealed that the descending artery was right asymmetric in 45.1% of specimens, left asymmetric in 50.4%, and bilaterally symmetric in 4.5% (Vogt *et al.* 2009). In the symmetric variant, two branches arise from the heart instead of one, pass the hindgut on both sides, and fuse underneath to run as unpaired vessel to the subneural artery.

Comparison of intra-individual FA and inter-individual SDV of a given trait in the same batch of marbled crayfish

revealed that FA is mostly smaller and not narrowly correlated with SDV. For instance, in 11 communally raised stage-5 batchmates the CVs of the number of aesthetascs on the 1st antennae and the number of corrugated setae on pereopods 1, 2 and 3 were 7.44%, 6.58%, 6.79%, and 5.61%, while the corresponding FA-values were 0.97%, 1.61%, 2.88%, and 2.55%. Görür (2009) made similar observations when investigating FA and inter-individual SDV of morphological traits in clonal cabbage aphid *Brevicoryne brassicae*.

5.3.2 *Phenotypic variation between homonomous metameres in segmented animals:* Information on developmental stochasticity was only rarely obtained from serially repeated body parts of homonomously segmented animals. An example is provided by Astauroff (1930), who compared the number of parapodial setae among more than 140 segments of the polychaete *Nephthys caeca* and the number of tarsal setae among 46 segments of the centipede *Geophilus ferrugineus*. After having normalized data across body length, there was still considerable variation in seta number per segment that fluctuated independently from the neighbouring segments. The author concluded from these data that each setagenic process has a certain degree of variability that is related neither to the genotype nor to the external environment.

5.4 *Suitability of colonial and polyphenic invertebrates for research on SDV*

Several sessile invertebrate groups such as the Porifera, Cnidaria, Bryozoa, and Tunicata use asexual budding to form colonies of genetically identical individuals. If such colonies are reared under controlled laboratory conditions that minimize environmental influences, then they can be used for research on SDV as well. Particularly attractive are colonies that have the individuals symmetrically arranged and that produce solid skeletal structures like many hydrozoans and bryozoans. As an example, Hageman *et al.* (1999) investigated six morphological characters in the bryozoan *Electra pilosa* (figure 8A) and found that the non-genetic and non-environmental residual variance can account for more than 50% of phenotypic variation, being the greatest for zooecium width. The authors suspected that this residual variation is attributable to developmental stochasticity. Likewise, Ponczek and Blackstone (2001) measured differences in morphological traits among isogenic polyps of laboratory-reared hydrozoans *Hydractinia symbiolongicarpus* and *Hydractinia carnea*.

Polyphenism, the production of two or more discrete phenotypes in a population, was not yet exploited for research on SDV. The best investigated models of polyphenism, the aphids and social insects (Simpson *et al.* 2011; Srinivasan and Brisson 2012), are not suitable because the various morphotypes are determined by differences in ploidy and feeding. Better suitable are polyembryonic wasps of the genus *Copidosoma*, which generate different morphs in the same genetic and environmental context. These endoparasitic insects produce up to 3000 genetically identical embryos from a single zygote comprising two morphologically distinct larval castes (Smith *et al.* 2010). One caste remains larval all the time and acts as soldiers, whereas the other caste develops into reproducing wasps. Caste differentiation is determined by intrinsic factors of the wasp's egg and early cellular asymmetry (Zhurov *et al.* 2004). Stochasticity in these processes may contribute to polyphenism and to phenotypic variation within castes (figure 8B).

6. Generation, mediation and limitation of SDV

In the previous sections I have shown that SDV occurs in all types of organisms and that its dimensions vary considerably between traits and species. This chapter deals with the sources of SDV, its dependency from the genetic and environmental contexts, its mediation by molecular epigenetic mechanisms, and its limitation by buffering mechanisms.

6.1 *Generation of SDV at different levels of biological organization*

SDV is produced by stochastic processes in cells, tissues, organs, and organisms. Stochasticity in the latter three may have its origin in intracellular stochasticity or may arise independently (Kilfoil *et al.* 2009). Here, I will present examples from bacteria and yeast for intracellular SDV and from animals for higher-level SDV. In plants, the SDV generating processes are just beginning to be identified (Meyer and Roeder 2014).

Many biochemical processes in the cell are inherently stochastic, particularly if small numbers of molecules are involved. Randomness in such reaction systems is inversely proportional to the square root of the number of participating particles (Meng *et al.* 2004). One of the highly stochastic cellular processes is gene expression, in which binding of transcription factors and polymerase is the result of random encounters (Elowitz *et al.* 2002; Kærn *et al.* 2005; Raser and O'Shea 2005; Casadesús and Low 2013). Moreover, transcription and translation occur in short bursts at random time intervals rather than in a continuous manner. A protein arising from stochastic gene expression can then lead to a cascade of stochastic downstream events. These sources of intracellular SDV occur in the protocyte, the cell type of archaeans and bacteria, and in the eucyte, the cell type of protists, fungi, plants, and animals. Further examples of SDV generating processes in the Prokaryota are bistability of metabolic pathways, antigen variation, chemotaxis,

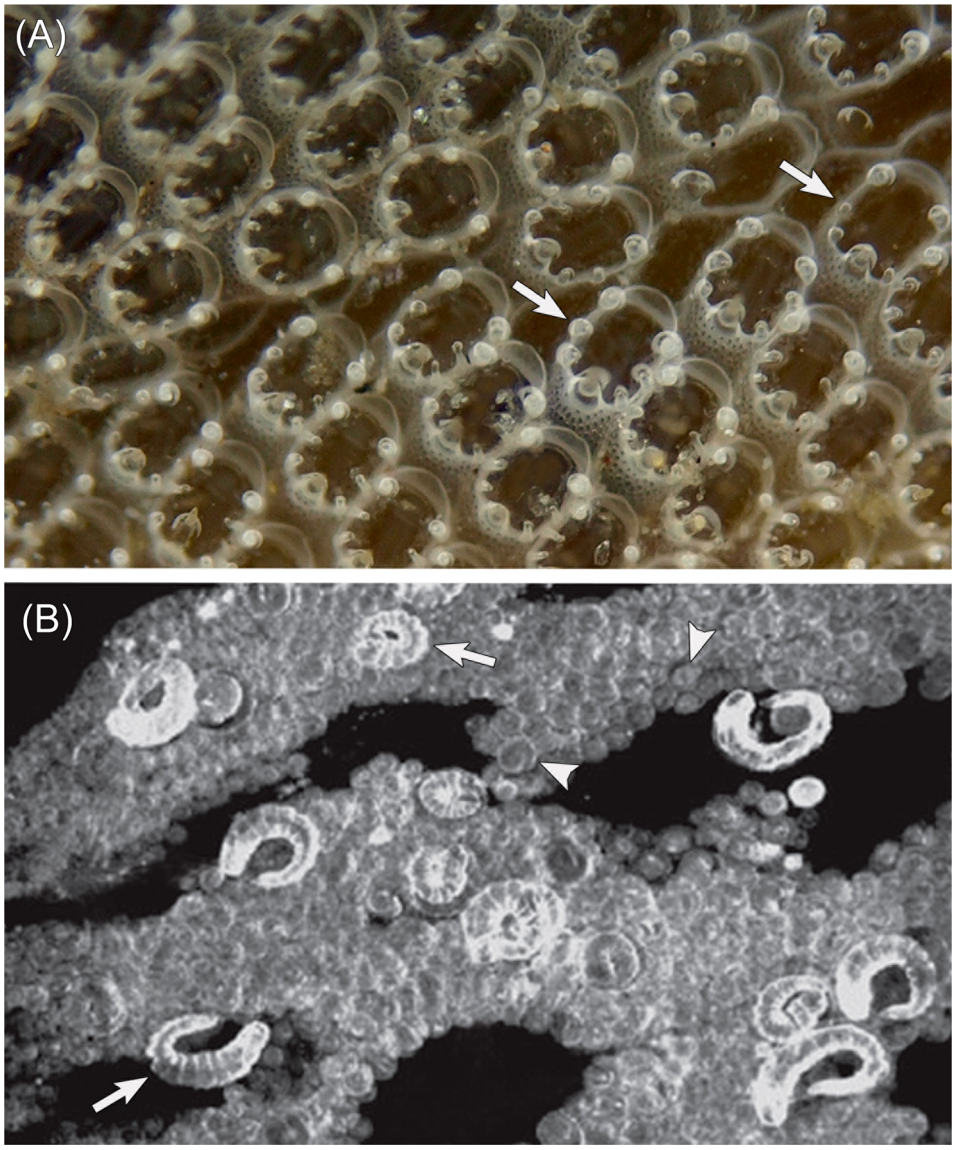

Figure 8. SDV in colonial and polyphenic invertebrates. (**A**) Colony of bryozoan *Electra pilosa* showing different morphology of asexually produced zooecia (arrows) (photo: David Fenwick). (**B**) Polymorula of polyembryonic wasp *Copidosoma bakeri* including hundreds of genetically identical precocious (arrows) and reproductive larvae (arrowheads) of different morphology. There is also phenotypic variation within each of the two larval types (from Smith *et al.* 2010).

ageing, and persistence against antibiotics (Davidson and Surette 2008; Balaban 2011).

The eucyte has further possibilities to generate intracellular SDV due to the possession of histone-associated chromatin, microRNAs, membrane-bound cell organelles, and the cytoskeleton. The histones and microRNAs enable variation of gene expression beyond the mechanisms described for prokaryotes (Bartel and Chen 2004; Brown *et al.* 2013). The cell organelles contribute to SDV by variation in number and spatial distribution, the latter being mediated by the cytoskeleton (Johnston *et al.* 2012). Another important source of SDV comes from the stochastic partitioning of the cell components between the daughter cells, which is particularly important for unicellular eukaryotes (Huh and Paulsson 2011). Further information on intracellular SDV and the underlying mechanisms in eukaryotes is found in Veitia (2005) and Raj and van Oudenaarden (2008).

In multicellular protists, fungi, plants and animals, additional SDV generators evolved with respect to cell differentiation, patterning, organogenesis, growth, reproduction,

behaviour, ageing, regeneration, and susceptibility to diseases. There are striking differences among the multicellular clades because of differences in body architecture, development, physiology, motility, and behaviour. For example, vascular plants are sessile and mechanically stable, have distinct stem cell systems with highly ordered proliferation patterns, are composed of dynamical patterning modules different from those of animals, and do not set aside germlines early in development as many animals do (Extavour and Akam 2003; Sablowski 2004; Barthélémy and Caraglio 2007; Hernández-Hernández *et al.* 2012). Animals, in contrast, are mostly motile and show sophisticated behaviours, which seem to be a particularly fertile source of SDV.

The involvement of SDV in differentiation and cell fate determination has been convincingly demonstrated for the slime mould *Dictyostelium discoideum*, one of the simplest models for studying cell differentiation. This amoebozoan forms temporary fruiting bodies composed of spore, stalk, and basal disc cells from a multicellular slug that originates from the aggregation of free-living amoebae. The CV of the fraction of cells that form the spores is mostly within 4.86%, whereas the contribution to stalk and basal disc cells is more variable, having CVs up to 24.5% and 100%, respectively (Nanjundiah and Bhogle 1995). Ràfols *et al.* (2014) established that the proportions of cells are strictly controlled above and below upper and lower thresholds but not in the range in between.

There are also several examples on the participation of SDV in cell fate decision in higher organisms (Balázsi *et al.* 2011). This process is usually interpreted as being deterministic; that is, cells acquire their fate by virtue of their lineage or their proximity to an inductive signal from another cell. In some cases, however, and in organisms ranging from bacteria to humans, cells choose one or another pathway of differentiation stochastically without apparent regard to neighbourhood or history (Losick and Desplan 2008). For example, animals use stochastic cell fate choices to govern priming of multipotent haematopoietic progenitor cells and to increase the repertoire of sensory and motor neuron subtypes (Chang *et al.* 2008; Johnston and Desplan 2010).

A prominent SDV generating mechanism in patterning is the stochastic expression of regulatory genes. Boettiger and Levine (2009) investigated the expression profiles of 14 developmental control genes in *Drosophila* embryos and found synchronous and stochastic patterns of gene activation. Synchronous genes displayed essentially uniform expression of nascent transcripts in all cells of an embryonic tissue, whereas stochastic genes displayed erratic patterns of *de novo* activation. Dietrich and Hiiragi (2007) found similar expression patterns during early embryonic development of mouse. Particularly, expression of Nanog, a transcription factor in embryonic stem cells that maintains pluripotency, exhibited a phase of random variability.

A particularly well investigated example of SDV during patterning is morphogenetic signalling. Medium- to long-distance morphogenetic signals are usually distributed as a gradient that is translated into more or less sharp boundaries (Nijhout *et al.* 2003; Veitia 2005). The nonlinear nature of such Turing reaction-diffusion and other patterning mechanisms (Turing 1952; Gierer and Meinhardt 1972; Murray 2003) is probably responsible for many differences among identically raised clonemates. Particularly impressive examples are the broad variation of spotted colour patterns in inbred guinea pigs, cloned Holstein cattle, and parthenogenetic marbled crayfish. Such nonlinear patterning mechanisms also contribute to the highly diverse colour patterns in sexually reproducing species like leopards, zebras, gastropods, or butterflies (Murray 2003; Nijhout *et al.* 2003; Meinhardt 2009). In embryos of vertebrates, the melanocytes originate in the neural crest and migrate from there to their final destination in the skin. Since this cell migration includes a considerable probabilistic component that increases with distance, variation of colour patterning is higher in the legs than in the proximity of the backbone (Seidel *et al.* 2003).

The malacostracan crustaceans, which include the marbled crayfish, are particularly good subjects to study SDV during organogenesis. They display a stereotyped cell division pattern, offering the possibility to study the relationship of cell lineage, gene expression, and organ development down to the single-cell level (Scholtz 1992; Dohle *et al.* 2004; Alwes and Scholtz 2006). By using the Distal-less protein as a marker, Dohle *et al.* (2004) revealed that in the amphipod *Orchestia cavimana*, corresponding limbs are formed by different genealogical cell lines, indicating nonlinearity of morphogenetic signalling. Stochasticity in organogenesis can also come from differences in the timing of cell cycles within expanding cell populations. As an example, in imaginal wing discs of *Drosophila melanogaster* cell synchrony is maintained over two to four doublings only (Milán *et al.* 1996). Transdetermination, the change in determined state in *Drosophila* imaginal discs, also includes SDV components due to the interaction of cell-autonomously and non-cell-autonomously induced signals (Maves and Schubiger 1998). Further examples of SDV in patterning and organogenesis are found in Kilfoil *et al.* (2009).

A largely neglected generator of developmental stochasticity is mechanical forces, which is particularly relevant for bigger animals and plants (Newman and Bhat 2007; Uyttewaal *et al.* 2012). Newman and Bhat (2007) discussed the interplay between molecular-genetic and dynamic physical processes in pattern formation of the vertebrate limb and assumed that the nonlinear physical processes contribute to SDV of limb traits in a manner similar to the nonlinear chemical processes. The broad variation of fingerprints in humans depends to a large degree on such nonlinear physical processes as well. The epidermal ridge pattern is

established between the 10th and 16th week of pregnancy as the result of buckling instability acting on the epidermis. This buckling process is controlled, among others, by shrinkage of the volar pads (Kücken 2007).

The production of SDV in adult animals is less well investigated than in earlier life stages although it may contribute much to ageing and diseases (Finch and Kirkwood 2000; Aranda-Anzaldo and Dent 2003; Martin 2014). Here, I would like to discuss three SDV producing mechanisms in more detail: stem cell proliferation, behaviour, and the allocation of metabolic resources. In the latter two, small differences between clonemates are thought to be generated by SDV and then be amplified by self-reinforcing circuitries.

In adult tissues, there is a balance between loss of cells and replacement by stem or progenitor cells. Stem cell proliferation includes stochastic components with respect to spatiotemporal activity, cell fate decision, and self-renewal. The latter relies upon cell-autonomous regulation (Simons and Clevers 2011). SDV also seems to be involved in the stimulation of cancer stem cell development via stochastic fluctuations in intercellular signalling (Dos Santos and da Silva 2013). Stochasticity generation by adult stem cells is more relevant for indeterminate than determinate growers because of the higher abundance and activity of stem cells in the former (Vogt 2012).

SDV of behaviour seems to be a particularly strong elicitor of phenotypic diversity. For example, the individual decision to eat a bit more or a bit less might first lead to slight differences in growth of clonemates, then to more pronounced differences in food uptake followed by further divergence in growth. Such self-reinforcing circuitries include behaviour, metabolism, and neuroendocrine feedback. They probably also drove the concomitant divergence of agonistic behaviour and growth observed in marbled crayfish batchmates raised without shelters.

Animals allocate their metabolic resources towards maintenance, growth, and reproduction. In adult marbled crayfish, growth periods and reproduction periods are alternating, and lost appendages are readily regenerated. Small initial differences in the allocation pattern among batchmates can lead to striking differences in future life history. For example, if a crayfish by chance loses one of his appendages, it may invest a higher proportion of energy and metabolites in regeneration, which may slow down growth and/or reproduction compared to its batchmates. On the other hand, a crayfish that by chance starts to reproduce earlier may grow to a smaller final size or live shorter than its batchmates.

So far, I have shown that SDV can be produced from the zygote to old age, but are there particularly sensitive life periods for SDV generation? The answer depends very much on the trait and the life history of the species considered. As a rule of thumb, embryonic development seems to be of prime importance in determinately growing mammals and insects, whereas the adult life period appears equally important in indeterminately growing crustaceans, molluscs, and fish. For example, in mammals differences in fingerprint patterns and spotting of the integument arise during the mid and late period of embryonic development and persist more or less unchanged throughout life (Kücken 2007; Caballero *et al.* 2012). In marbled crayfish, differences in marmoration start to develop in late embryogenesis and increase throughout the approximately 25 juvenile and adult moultings (Vogt *et al.* 2008). Likewise, differences in body weight among littermates of inbred rat were shown to have their roots in stochastic events in the zygote and first cleavage stages (Gärtner 1990, 2012), whereas in marbled crayfish such differences are more attributable to SDV generation in the adult life. SDV-related differences in ageing and diseases may have their origins in both early development and the later life (Aranda-Anzaldo and Dent 2003; Kirkwood *et al.* 2005; Vogt *et al.* 2008; Vogt 2010; Martin 2014).

6.2 *Dependency of SDV from the genetic and environmental contexts*

Although SDV is a non-genetic and non-environmental source of phenotypic variation, its absolute values and ranges are dependent on the genetic and environmental contexts. The relationship between SDV and the genetic background is easiest demonstrated by comparison of a given trait between species from different higher taxa. For instance, the range of longevity in a group of marbled crayfish was 437–910 days, whereas it was 3–31 days in a colony of the nematode *Caenorhabditis elegans*. Another example is provided by Gärtner (1985), who measured different ranges of SDV in six identically reared but genetically different lineages of inbred rat. Further evidence comes from the comparison of the CVs of different traits in the same group of animals, which varied from less than 1% to more than 100% in an armadillo quadruplet (Storrs and Williams 1968). These differences are supposedly the result of the modular architecture of animals and the semi-independency of the modules (Wagner *et al.* 2007). Finally, yet importantly, it has been shown that genetic mutations can change the range of stochastic variation in gene expression (Miller-Jensen *et al.* 2013; Richard and Yvert 2014).

The dependency of SDV from the environmental context must not be confused with the environmental proportion of phenotypic variation, which is usually expressed as the norm of reaction (Schlichting and Pigliucci 1998). A good example of the dependency of SDV from the environmental context was published by Gärtner (1985). He measured considerable differences in SDV of kidney weight among groups of rats that were genetically identical and of the same

gender and age but raised in different environments. These examples indicate that the genetic and environmental contexts provide a framework for SDV that is newly adjusted when the genome or the environment changes.

6.3 *DNA methylation as an example for the molecular mediation of SDV*

As outlined previously, there is already a bulk of information on the SDV generating processes but the underlying molecular mechanisms are only poorly understood. Among the mechanisms that mediate the production of different phenotypes from the same genotype is DNA methylation, which is effective in all organisms from bacteria to man (Rakyan *et al.* 2002; Jaenisch and Bird 2003; Feinberg and Irizarry 2010; Casadesús and Low 2013). Alteration of this chromatin modification, either stochastically or by the input of environmental signals, can change gene function and result in phenotypic variation (Jaenisch and Bird 2003; Weigel and Colot 2012).

The mediating role of DNA methylation is better investigated for environmentally induced phenotypic plasticity than for SDV and comes from laboratory and field studies. For example, Lyko *et al.* (2010) analysed DNA methylation at single-base-pair resolution in honeybee queens and workers and found variation of the methylation pattern in more than 500 genes. They concluded that the phenotypic differences between the two morphotypes that is caused by different feeding is implemented in concert with DNA methylation. Liebl *et al.* (2013) investigated genome-wide DNA methylation in expanding populations of house sparrow *Passer domesticus*, which was introduced to Kenya in the 1950s. They found high levels of variation in methylation across the genome and a negative correlation between epigenetic and genetic diversity, suggesting that DNA methylation mediates the observed phenotypic plasticity. Bossdorf *et al.* (2010) manipulated the DNA methylation pattern in *Arabidopsis thaliana* and revealed dramatic impacts on ecologically important traits and their variability.

To my best knowledge, genome-wide analysis of DNA methylation at single-base-pair resolution, the most sensitive method available, has not yet been applied to SDV. However, other approaches like the correlation of the methylation pattern of specific genes with phenotypic variation have already been utilized. For example, Field and Blackman (2003) demonstrated that the stochastic loss of resistance to an insecticide in clonemates of the peach-potato aphid *Myzus persica* was caused by changes in methylation of the esterase genes. Rakyan *et al.* (2002) found that the agouti viable yellow allele A^{vy}, which underlies different coat colours in isogenic mice, could stably exist in several epigenetic states. These states are established during early embryogenesis by stochastic DNA methylation events and can be transgenerationally inherited. Kaminsky *et al.* (2009) analysed epigenetic metastability of ~6000 genomic regions in human monozygotic twins and concluded that stochastic epigenetic variation is probably more important than environmental variation to explain phenotypic differences among monozygotic twins.

6.4 *Limitation of SDV by buffering mechanisms*

SDV would probably produce a bewildering array of phenotypes from the same genotype if it were not counteracted by control mechanisms. Researchers working on SDV of unicellular organisms usually speak of 'noise control' (Kim and Sauro 2012), whereas researchers working on multicellular organisms speak of 'developmental buffering' (Debat and David 2001; Patterson and Klingenberg 2007). Control of SDV includes feedback loops, redundancy and modularity, clustering of genes with similar noise, and specific activities of control genes and control molecules (Klingenberg 2003, 2006; Kitano 2004; Levy and Siegal 2008; Wang *et al.* 2011).

In bacteria, negative and positive feedback loops and feedforward loops are apparently of prime importance for noise control (Jablonka and Raz 2009; Kim and Sauro 2012; López-Garrido *et al.* 2012). In pathogenic bacteria, such loops often lead to an infective and a non-infective phenotype (Smits *et al.* 2006). Similar feedback loops are also effective in eukaryotic cells. Nanjundiah and Bhogle (1995) and Ràfols *et al.* (2014) explained SDV in cell differentiation of the social amoeba *Dictyostelium discoideum* by cell-autonomous positive feedback and global negative feedback. Zordan *et al.* (2006) investigated stochastic switching between white and opaque phenotypes of the human fungal pathogen *Candida albicans*, which differ in morphology, gene expression, and infectivity, and found that stabilization of these phenotypes involves a self-sustaining positive feedback loop. Once activated, this loop persists for several generations. Avendaño *et al.* (2013) investigated the galactose uptake system of yeast and found that positive feedback loops stabilize different phenotypic states, whereas negative feedback loops allow tuning of the range and transition rates between phenotypic states.

Another mechanism for control of SDV in bacteria and yeast is grouping of genes with similar noise. Investigations in *Escherichia coli* and *Saccharomyces cerevisiae* revealed that proteins and their coding genes can vary considerably with respect to SDV. Essential proteins like those involved in protein synthesis have low noise and less-essential proteins like those responding to environmental changes have high noise under multiple conditions, suggesting that SDV of proteins has been selected during evolution (Fraser *et al.* 2004; Newman *et al.* 2006). In yeast, persistently open chromatin domains are apparently preferred sites for

clustering of essential genes as they enable noise reduction by avoidance of transcriptional bursting associated with chromatin remodelling (Batada and Hurst 2007).

In multicellular organisms, developmental buffering is often subdivided into canalization, the buffering against genetic and environmental variation, and developmental stability, the buffering against stochastic developmental variation. The relationship between canalization and developmental stability was subject to debate in the past. Some authors have suggested that there is only one mechanism accounting for developmental homeostasis, while the majority of authors have proposed two independent processes that are somehow linked to each other (Debat *et al.* 2000; Milton *et al.* 2003; Breuker *et al.* 2006).

In the last decade, some genes with buffering function have been identified in animals and plants. For example, cyclin G, a regulator of transcription and cell cycle, plays a major role in developmental stability of *Drosophila melanogaster*, suggesting that phenotypic robustness can be strongly influenced by individual genes (Debat and Peronnet 2013). Another example is the gene ERECTA, which contributes to canalization of rosette leaf number in *Arabidopsis thaliana* under long-day photoperiod (Hall *et al.* 2007).

SDV-buffering molecules include signal transduction proteins, heat shock proteins, and microRNAs. An example of the former is Wnt, which filters SDV during development and pattern formation (Arias and Hayward 2005). Heat shock protein Hsp90 was the first protein identified to be involved in developmental buffering (Queitsch *et al.* 2002; Milton *et al.* 2006; Sangster *et al.* 2008). It is one of the most abundant proteins expressed in cells, is well known as a chaperone of many regulatory proteins, and can canalize phenotypes by suppressing the underlying genetic and epigenetic variation in a trait specific manner (Milton *et al.* 2003; Patterson and Klingenberg 2007; Salathia and Queitsch 2007). Meanwhile, other heat shock proteins have been shown to be involved in developmental stability as well (Takahashi *et al.* 2010). Knockdown of Hsp67Bc and Hsp22 significantly increased fluctuating asymmetry of bristle numbers in *Drosophila melanogaster*, and knockdown of Hsp67Ba increased both FA and inter-individual variation of wing shape.

MicroRNAs are abundant gene-regulatory molecules constituting almost 1% of the genes in animal genomes. They repress the expression of protein-coding mRNAs through binding of a minimal-recognition sequence and are key players in noise control (Herranz and Cohen 2010; Shomron 2010). They are also involved in differential expression of homologue alleles within cells and incomplete penetrance, contributing to the lack of genotype-to-phenotype correlation (Ahluwalia *et al.* 2009). Hornstein and Shomron (2006) assumed that the interaction of microRNAs with the network of protein-coding genes evolved to buffer stochastic perturbations, thereby conferring robustness to developmental programmes. Li *et al.* (2009) found that miR-7, which is widespread in animals, functions in several feedback and feedforward loops, and is essential to buffer these regulatory systems against environmental perturbations. Osella *et al.* (2011) modelled the buffering role of microRNA-mediated feedforward loops, in which a master transcription factor regulates a microRNA and, together with it, a set of target genes.

If DNA methylation is an important mediator of SDV as outlined above, then proteins involved in the establishment and erasure of the methylation patterns and their interpretation should play a role in the control of SDV as well. These are the DNA methyltransferases that mediate cytosine methylation (Goll and Bestor 2005), the recently discovered ten-eleven translocation enzymes that mediate DNA demethylation (Kohli and Zhang 2013), and the methyl-CpG binding domain proteins that play an important role in interpreting the genetic information encoded by methylated DNA (Zou *et al.* 2012).

7. Implications of SDV for genotype-to-phenotype mapping, individuality, and personality development

There is no doubt that an individual DNA-sequence has the capacity to map to different phenotypes. This is impressively shown by the origination of more than 400 structurally and functionally different cell types from the single genome of the zygote in humans (Vickaryous and Hall 2006). It is also well known that a genotype *sensu strictu* can translate into multiple phenotypes under different environmental conditions (Scheiner 1993; Nanjundiah 2003; Pigliucci 2010). For instance, if genetically identical stolons of the same plant are grown at different altitudes or in different soils they usually develop different morphologies, and when diploid honeybee larvae are fed on either royal jelly or pollen they develop into morphologically and functionally distinct queens and workers, respectively (Schlichting and Pigliucci 1998; Simpson *et al.* 2011).

Despite of these examples on the plasticity of the genotype, it is widely believed that in a given environment a genotype produces one phenotype only. However, laboratory experiments with clonal organisms in standardized environments have clearly shown that even under these conditions, multiple phenotypes are produced from a single genotype, thanks to SDV. This finding corroborates that the very nature of genotype-to-phenotype mapping is not one-to-one but one-to-many. Newman and Müller (2000) argued that in animals the relationship of genotype and phenotype was looser in their early evolution than today and became constrained only by the evolution of canalization, in which

an 'over-determining' genetic circuitry ensures that changes of intrinsic or extrinsic variables have less impact on the morphological outcome.

The concept of an individual is vague in biological philosophy (Buss 1987; Wilson 2007; Kupiec 2009). Paradigmatic biological individuals are members of a population that are distinct from others. Wilson (1999) distinguished six different concepts of individuality: an individual can be a particular, a historical entity, a functional individual, a genetic individual, a developmental individual, or a unit of selection. Some authors extended the term 'individuality' even to other distinct entities of life that may act as units of natural selection such as genes, cell organelles, cells, developmental patterns, functional modules, life cycles, and even colonies, populations and species as discussed in Lewontin (1970), Hull (1980) and Gould and Lloyd (1999). Interestingly, SDV can contribute to variation of all of these aspects of individuality up to the level of the organism, with the exception of genetic individuality, which is the realm of genetic variation.

The processes that generate differences among individuals have been discussed for more than a century in the framework of the nature–nurture debate (Galton 1876; Overton 1973; Fox Keller 2010). This debate was spurred by biologists, social scientists, and politicians and was the basis for the paradigm clash between genetic determinism and Lysenkoism, among others. Traditionally, members of sexually reproducing populations are considered as distinct individuals because of genetic differences, whereas members of asexually reproducing populations are seen as identical copies. However, thanks to SDV, members of clonal populations must be regarded as distinct individuals as well. They are not genetic individuals but morphological and functional individuals. This even holds for bacteria as revealed by single cell analyses (Avery 2006; Ackermann 2013; Nikel *et al.* 2014), suggesting that individuality is a general attribute of all living beings.

The observation of SDV-caused individuality in clones of unicellular organisms served as a stimulus to interpret the tissues and organs of multicellular organisms as structural and functional mosaics instead of uniform entities (Woods 2014; Yvert 2014). This insight has considerable consequences for our understanding of diseases and may constrain highly publicized personalization of medicine by genomic approaches (Chan and Ginsburg 2011).

The term personality refers to behaviour-based peculiarities that differ across individuals and, once established, remain relatively consistent over time (Stamps and Groothuis 2010). It is probably the most complex and most variable trait, at least in higher mammals. It has been seen for long as an exclusive feature of humans because it was thought to require a complexity and subtlety that is unique to man (Bell 2007), but in recent years the concept of personality has been extended to animals as well (Stamps and Groothuis 2010; Trillmich and Hudson 2011). Understanding of the relative contribution of genetic and non-genetic factors in shaping personality traits is of fundamental interest to biologists, psychologists, and social scientists (McCrae *et al.* 2001).

Gosling (2008) emphasized that due to easier genetic manipulation and standardization of the living conditions animal studies may provide unique opportunities to disentangle the genetic, environmental, and stochastic developmental bases of personality and to study personality changes with age and disease. The stochastic developmental proportion of personality is best investigated with clonal animals. Experiments with inbred mice, cloned pigs, and parthenogenetic pea aphids and marbled crayfish have shown that SDV can cause personality differences among isogenic batchmates, indeed (Archer *et al.* 2003b; Vogt *et al.* 2008; Lewejohann *et al.* 2011; Schuett *et al.* 2011). Particularly impressive is the marbled crayfish example, in which batchmates diverged into dominants, subdominants, and subordinates despite shared environmental conditions and initially identical size and behaviour (Vogt *et al.* 2008).

In monozygotic human twins, the non-shared environment is often seen as the main cause of differences in personality, cognitive abilities, and psychopathology (Plomin and Daniels 1987; Plomin 2011). However, Turkheimer and Waldron (2000) did not find such a correlation in their data and suspected developmental instability as a major causative factor. Molenaar *et al.* (1993) also argued that there must be a third source of variation in addition to genetic and environmental factors coming from nonlinear epigenetic processes and creating variability at all phenotypical-somatic and behavioural levels. The authors also introduced a model to quantify these influences.

Behaviour and the brain are the main foundations underlying personality in animals and humans (LeDoux 2002; Canli 2006). Behaviour is central to personality by definition and the brain is the final pathway through which genetics, environmental influences, and stochastic developmental factors operate together (Van Praag *et al.* 2000; Davidson 2001). Interestingly, the degree of SDV is particularly high in behaviour and wiring and functioning of the brain (Clarke 2012). Therefore, personality development could hardly be forecasted even if the DNA sequence of an individual and its future living conditions were known.

The significant contribution of SDV to personality also has implications for the ethical debate on reproductive cloning of humans (Elliott 1998; Brock 2002). Brock (2002) raised concerns that cloning of humans might undermine our sense of self, the value of human beings, and the freedom to construct the own life because of the presence of an earlier twin. These arguments against human cloning can be refuted because, due to SDV, clones will never have the same

personality as their donors or earlier clonemates. Nevertheless, cloning of humans and animal companions still makes little sense because what are desired are copies of the personality and not just of the form of the beloved person or pet. Because of the high proportion of SDV in personality development, human or animal personalities cannot be eternalized and vanish with the death of the individuals.

8. Implications of SDV for applied biology and medicine

SDV affects several fields of applied biology and medicine including animal and plant production, breeding of beneficial microbial strains, pharmaceutical and toxicological testing, infectivity and resistance of pathogens, and progression and treatment of non-infectious diseases.

8.1 *Impact of SDV on animal and plant production, biotechnology, and biological testing*

In applied animal biology, SDV is usually perceived as a nuisance biasing attempts to produce standardized animals for husbandry, aquaculture, and animal testing. The first method developed to produce homogeneous animals was inbreeding but even in highly inbred strains, the degree of phenotypic variation remained remarkably high due to SDV (Gärtner 1990). Later, cloning methods like twinning and somatic cell nuclear transfer were developed as the ultimate tool to create copies of a desired phenotype and to average out individual variation. Contrary to expectation, such clonemates were phenotypically variable as well, which was often attributed to insufficiencies of the cloning technique (Jaenisch and Bird 2003; Smith and Murphy 2004). However, a considerable proportion of this phenotypic diversity is obviously caused by SDV and would persist even after perfecting the cloning technique. It depends very much on the target trait and expectation of the customer whether cloning of animals is useful or not. For example, cloning is a rather successful approach to increase milk yield in cattle because SDV of this trait is relatively small (Seidel 2002) but it is rather unsuitable to copy pets with attractively spotted integuments (Shin *et al.* 2002) because SDV of this trait is very high.

In plant production, SDV is perceived as a nuisance as well if valuable strains are to be propagated in true-to-type form. The clonal multiplication of plants from cultured cells and tissues was expected to solve this problem, but contrary to expectation, phenotypic variation persisted or was even increased, which is called somaclonal variation (Karp 1994; Miguel and Marum 2011). Meanwhile, it is well known that the degree of SDV is often higher in animal and plant cell cultures than in the respective source organs. Rubin (1990) explained this phenomenon with the absence of buffering effects exerted by higher levels of organization. The disturbing effects of SDV in cell culture could be reduced if the sources of SDV and their buffering mechanisms were better known (Pilbrough *et al.* 2009). On the other hand, SDV may be exploited to improve crop or to develop new flower varieties (Karp 1994). The same holds for bioreactors, in which SDV usually generates microbial heterogeneity (Patnaik 2006; Delvigne and Goffin 2014).

In biological tests for drug development and chemical risk assessment SDV has been feared for long as a disturbing factor (Gärtner 1990; Adelman 2005). Such tests are routinely performed with genetically identical organisms like inbred mice and rats or parthenogenetic water fleas. They are the basis for the calculation of threshold values like ‘threshold of toxicological concern’, ‘no-observed-effect level’, or ‘acceptable daily intake’ (Kroes *et al.* 2000). Such values are often mandatory by law but due to the SDV-related fuzziness inherent to the test organism, they should be regarded as guidance values rather than the absolute truth. Adelman (2005) stressed that the susceptibility to toxic exposure is highly variable from person to person not only because of genetic differences and different living conditions but also because of SDV, and that environmental law should consider this variation.

8.2 *Impact of SDV on virulence and resistance of pathogens, and medication of diseases*

The prime disease agents of humans and animals are asexually reproducing viruses, bacteria, protists, and fungi with clonal population structures (Tibayrenc and Ayala 2012). For example, 72% of the 179 known eukaryotic human pathogens and parasites are clonal, affecting more than 1339 million people worldwide (De Meeûs *et al.* 2009). The same holds for agricultural pests like mitosporic fungi and parthenogenetic insects (Taylor *et al.* 1999; Hoffmann *et al.* 2008), which cause high yield losses and considerable costs of pest control. Worldwide, approximately 3 million tons of pesticides with a purchase price of US$ 40 billion are annually applied (Pimentel 2005).

In order to optimize virulence and to evade immune surveillance, clonal disease agents and pests produce phenotypic diversity at their cell surface either by genetic or epigenetic mechanisms (Avery 2006; Verstrepen and Fink 2009; Casadesús and Low 2013). The role of genetic variation in pathogenesis is much better investigated than the role of stochastic or environmentally induced epigenetic variation (Calo *et al.* 2013). Whether the genetic or epigenetic sources of phenotypic variation are predominant seems to depend very much on the pathogen. For example, the gastric-ulcers-causing *Heliobacter pylori* and the gonorrhoea-causing *Neisseria gonorrhoeae* show rapid genetic changes, whereas

the plague-causing bacterium *Yersinia pestis* and the typhus-causing *Salmonella enterica enterica* ser. Typhimurium are essentially a single clone (Maynard Smith *et al*. 1993; Spratt 2004). Consequently, the latter depend much more on SDV than the former to enhance infectivity. Freed *et al.* (2008) revealed that the genomic fragments that conferred the highest levels of SDV in *Salmonella* were promoters controlling the synthesis of flagella, which are essential for host–pathogen interactions and virulence.

Further medical topics, in which SDV is involved, are the resistance of disease agents against antibiotics and the latency of viruses. In bacteria, there are two types of resistance: the first and better-known type relies on stable genetic changes caused by recombination and mutation, and the second type relies on stochastic epigenetic alterations (Dhar and McKinney 2007). The escapers of the latter category are called 'persisters' and their refractoriness to antibiotics is often metastable and transient. The self-induced transient resistance to antibiotics in *Dictyostelium discoideum* observed by Kasbekar *et al*. (1985) seems to have an SDV component as well. Patra and Klumpp (2013) assumed that phenotype switching in isogenic bacterial pathogens is mostly a stochastic epigenetic process independent of the environment and provided a theoretical framework to explain this phenomenon. Adam *et al.* (2008) investigated the evolution of SDV-based resistance against antibiotics in *Escherichia coli* and found that variant gene expression patterns in an isogenic population were epigenetically mediated, inherited, and preserved for multiple generations. In pathogenic viruses, fate decision between lysogeny and latency is controlled by stochastic gene expression in key auto-regulatory proteins as shown for HIV-1 (Singh and Weinberger 2009).

SDV is also involved in the onset and progression of non-infectious diseases including psychiatric disorders and cancer (Woolff 1997; Bosl and Li 2010; Feinberg and Irizarry 2010). For instance, intra-tumour heterogeneity, the ability to seed metastases, and the survival of tumour cells to therapy are often associated with stochastic variation of DNA methylation (Hansen *et al.* 2011; Marusyk *et al.* 2012). SDV is also at play during ageing and is seen important for the understanding of processes that lead to age-related frailty, disability, and disease (Finch and Kirkwood 2000; Kirkwood 2012). Moreover, SDV is suspected to account for the non-uniform response of the diseased cells of an organ to pharmaceuticals, which impedes medication (Niepel *et al.* 2009).

A better understanding of the causes and mediation of SDV could facilitate the fight against pathogens and the therapy of non-infectious diseases. It may help to reduce the fraction of non-responding pathogens and to sensitize higher percentages of diseased cells to therapeutic intervention. Proposals on the reduction of SDV were made by Heithoff *et al.* (1999), Davey Smith (2011), Miller-Jensen *et al.* (2013), and Pujadas and Feinberg (2012). For example, Miller-Jensen *et al.* (2011) studied how chromatin modifications modulate gene expression noise and argued that this fundamental information can be applied to develop innovative therapies against 'pathogenic noise'. Heithoff *et al.* (1999) presented evidence for an essential role of stochastic DNA adenine methylation in virulence of salmonellae and suggested DNA adenine methylase inhibitors as therapeutic agents.

9. Implications of SDV for ecology

The consequences of SDV for genotype-to-phenotype mapping, individuality, and applied biology and medicine discussed in the previous sections were based on sound experimental evidence. The ecological and evolutionary implications of SDV outlined in the following are inferred with some plausibility from laboratory experiments and are exemplified by clonal populations. In sexual populations and in the complexity of natural habitats, it is difficult to keep genetic variation, environmental variation and SDV apart. In this section, I will discuss the role of SDV as a bet-hedging strategy in fluctuating environments, as an epigenetic chance generator and source of functional biodiversity, and as a facilitator of social interactions in clonal groups.

9.1 *SDV as a bet-hedging strategy to cope with environmental uncertainties*

Animals in the wild are often confronted with changing environments. They cope with such challenges either by the *a priori* production of phenotypes without knowing the future conditions (bet-hedging) or by the *a posteriori* alteration of phenotypes in response to environmental signals. Populations apply the latter strategy when there are reliable informational cues about the long-term state of the environment and the former strategy in unpredictable environments that lack such cues (Beaumont *et al.* 2009; Childs *et al.* 2010; Libby and Rainey 2011). Bet-hedging is a risk spreading strategy that enhances the probability of survival at the expense of a lowered arithmetic mean fitness (Ripa *et al.* 2010; Starrfelt and Kokko 2012). It is effectuated by genetic recombination, random mutation, or SDV. Genetic recombination is particularly important in sexually reproducing populations and SDV in asexual populations (Barton and Charlesworth 1998; Thattai and van Oudenaarden 2004; Acar *et al.* 2008; Veening *et al.* 2008). López-Garrido *et al.* (2012) emphasized that epigenetic bet-hedging (SDV) may be less risky for organisms than random mutation because increased mutation rates may involve a burden incompatible with adaptation.

At first glance, SDV related bet-hedging seems to be of minor significance in ecology because the asexuals as the main benefiters are apparently outnumbered by the sexually reproducing species. However, in bacteria and protists,

asexual reproduction is the rule. Fungi and plants mostly combine sexual and clonal reproduction and the balance between the two varies widely between and within species (Taylor *et al.* 1999; Eckert 2002). For example, clonal or vegetative reproduction was found in 66.5% of the central European vascular plants, and in 112 vegetation types investigated, the frequency of clonal plants exceeded that of non-clonals (De Kroon and van Groenendael 1997). In animals, asexual reproduction is common in several higher taxa including the sessile sponges, cnidarians, bryozoans and ascidians and the parasitic trematodes and cestodes. Moreover, agricultural pests like the aphids and key species of aquatic food chains like the daphnids often reproduce by facultative parthenogenesis (Suomalainen *et al.* 1987; Vrijenhoek 1998; De Meeûs *et al.* 2007; Schön *et al.* 2009).

SDV might also play an important role in the invasion of new environments because invasive populations are often small and genetically impoverished. However, despite of these constraints they can be ecologically and evolutionarily very successful (Tsutsui *et al.* 2000). This phenomenon is well known as 'invasion paradox' but the underlying mechanisms are only poorly understood (Fridley *et al.* 2007). Invasive species are regarded as a major factor for the loss of biodiversity and modern environmental damages (Davis 2009). For example, in the United States, UK, Australia, South Africa, India, and Brazil together, alien plants, animals, and microbes were estimated to cause costs in damages and control of more than US$ 300 billion per year (Pimentel *et al.* 2001). Therefore, it is of prime importance to understand how invading species generate enough phenotypic variation to survive in new geographic areas and to extend ranges (Sakai *et al.* 2001; Davis 2009). The first steps of invasion, survival of the invading specimens and establishment of a founder population, seem to depend on epigenetic rather than genetic variation (Riis *et al.* 2010; Liebl *et al.* 2013), and SDV may be an important contributor to this epigenetic variation.

9.2 *SDV as an epigenetic chance generator and source of functional biodiversity*

The structure and dynamics of populations, the central units of ecology and evolution, are determined by the genetic chance generators random mutation, recombination, and drift, among others (Falconer and Mackay 1996; Lande *et al.* 2003; Beatty 2006, 2010; Lenormand *et al.* 2009; Koonin 2012). Studies on clonal populations in the laboratory and human twins revealed that there is a further epigenetic-based chance generator, namely SDV (Finch and Kirkwood 2000; Fraga *et al.* 2005; Vogt *et al.* 2008; Martin 2009; Czyz *et al.* 2012). SDV is probably effective in all populations but is particularly relevant when genetic variation is absent as in asexual populations or rather ineffective as in bottlenecked and small invasive populations.

Two examples of the marbled crayfish may give an idea on the influence of SDV on population structure and dynamics. In the first experiment, seven isogenic batchmates were reared communally for more than 550 days, and growth and egg-laying were regularly monitored. SDV of these life history traits caused repeated relative position changes of specimens within the group (figure 9A). For example, regarding total length, specimen S5 was number 5 at day 258, number 1 at day 365 and number 2 at day 558. In the second experiment, stage-3 batchmates from the same mother were divided into two groups of 10 and then raised under identical conditions for 312 days. Interestingly, the spectra of growth variation developed differently in the two groups. At the beginning of the experiment, CVs of carapace length were similar (2.92% versus 3.23%), diverged maximally at day 155 (26.7% versus 6.70%) and converged again until day 312 (24.6% versus 12.8%) (figure 9B).

SDV affects all kinds of traits but only some of them are ecologically and evolutionarily important fitness traits. The difficulty to discriminate between fitness traits and non-fitness traits has repeatedly been discussed (Mills and Beatty 1979; Ariew and Lewontin 2004), but at least camouflage, longevity, and the number of offspring per female can be regarded as fitness traits. These traits were shown to vary markedly among batchmates of marbled crayfish (table 2; figure 5E). In the case of camouflage, the fitness trait is probably marmoration itself and not the detailed arrangements of the pigment spots. This interpretation is supported by information on coat coloration in cats and dogs, which possess genes for solid coat, piebald spotting, and so forth, but no genetic instruction for the spatial distribution of individual motifs (Kaelin and Barsh 2013). The high degree of SDV in colour patterns, fingerprints, noseprints, and irises may be explained by assuming that these traits have neither adaptive nor maladaptive values and that the cost for their buffering is saved. SDV generates fitness variation also in unicellular organisms as shown by Wang and Zhang (2011) for stochastic gene expression in yeast.

According to common belief, it does not matter which of the members of an asexual population reproduces because all individuals are expected to yield the same progeny. This assumption would only be correct if the genes were the sole determinants of phenotype. However, if the clonal reproducers were epigenetically and phenotypically diverse due to SDV, then the future structure and performance of a population would very much depend on which specimens contribute to the next generation, resembling the situation in sexually reproducing populations.

SDV can create 'functional biodiversity' via epigenetic variation and can thus be an important driver of population

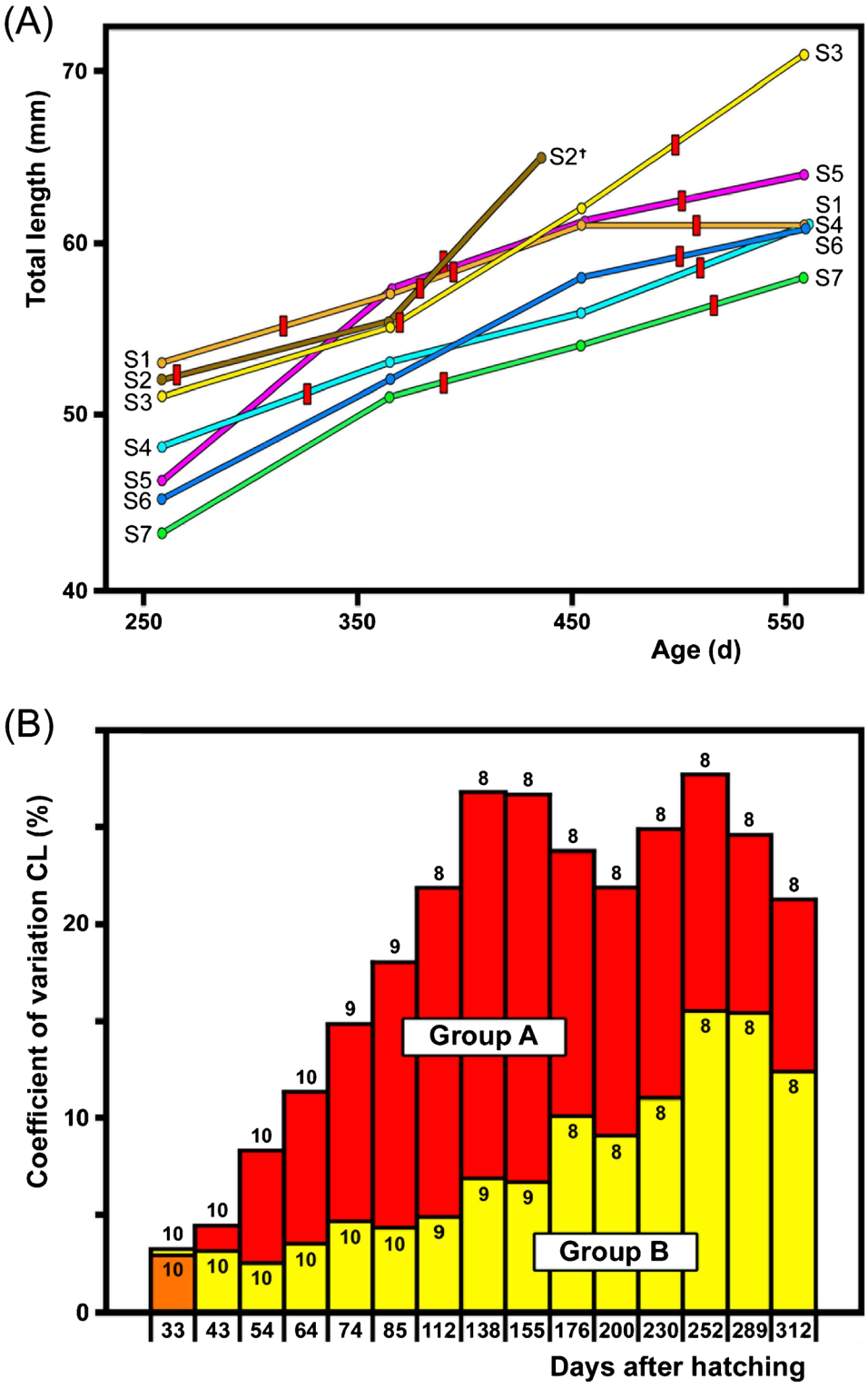

Figure 9. SDV as an epigenetic chance generator in cultured populations of marbled crayfish. (**A**) SDV-caused position changes of individuals in a communally raised population of seven batchmates (S1–S7). Individual profiles of growth and reproduction were monitored for more than 300 days. Red vertical bars indicate time of oviposition (from Vogt *et al.* 2008). (**B**) Differences of SDV of growth in subpopulations from the same batch. Stage-3 juveniles were removed from their mother, randomly divided into two groups of ten, and then raised under identical conditions for 300 days. Note fluctuation of CV of carapace length (CL) over time in each group and differences in dimension and fluctuation pattern between groups. Figures on bars indicate number of specimens (from Vogt *et al.* 2008).

and ecosystem functioning similar to environmentally induced epigenetic variation (Smith *et al.* 2011; Latzel *et al.* 2013; Medrano *et al.* 2014). There is experimental evidence that SDV can modify factors such as fitness and biomass, at least in clonal populations. For example, Smith *et al.* (2011) investigated the influence of SDV on 12 leaf traits in eight natural clones of quaking aspen, *Populus tremuloides*, over the 160-year life span and found increases of phenotypic diversity with age. They concluded that this developmental source of phenotypic variation might enhance clonal fitness and partially underlie aspen's ability to tolerate the large environmental gradients in its broad geographical range. Latzel *et al.* (2013) performed greenhouse experiments with epigenetically diverse populations of *Arabidopsis thaliana* and found that they produce up to 40% more biomass than epigenetically uniform populations. The positive effects of epigenetic diversity were strongest when populations were grown together with competitors or infected with pathogens.

The importance of SDV or environmentally induced epigenetic differences as a source of phenotypic diversity in sexually reproducing populations has recently been demonstrated by Medrano *et al.* (2014). These authors investigated the relationship between epigenetic variation and functional plant diversity by conducting epigenetic and genetic marker-trait association analyses for 20 traits in the perennial herb *Helleborus foetidus* from 10 sampling sites in southeastern Spain. They revealed greater epigenetic than genetic diversity and concluded from their results that epigenetic variation can be an important source of intraspecific functional diversity, facilitating exploitation of a broader range of ecological conditions.

9.3 *SDV as a facilitator of social interactions in clonal populations*

Despite genetic identity, parthenogenetic animals can establish social hierarchies as shown for geckos, lizards, and marbled crayfish (Case 1990; Bolger and Case 1992; Vogt *et al.* 2008; Farca Luna *et al.* 2009). Establishment and maintenance of social hierarchies requires individual recognition of group members either by optical or chemical cues (Wilson 1975). Such individual signatures can obviously be generated by SDV as exemplified by marbled crayfish, which have individual spotting patterns and probably individual urine signatures. The latter indicate the status of aggressiveness in crayfish and are respected by conspecifics (Breithaupt and Eger 2002).

In some clonal populations of microorganisms, SDV can generate different phenotypes that perform diverse functions for the benefit of the population, for example during pathogenesis or in biofilms. Ackermann *et al.* (2008) established that in pathogenic bacteria SDV can promote the formation of a subpopulation that releases enzymes by lysis, preparing the ground for a successful infection. The remaining bacteria benefit from this self-destructive cooperation, invade the host, and proliferate. This cooperative strategy differs from bet-hedging with respect to the benefits for the population: in bet-hedging, the benefits arise when the environment fluctuates, whereas in social cooperation the benefits come from the enhancement of fitness and the gain of new functionality (Avery 2006; Ackermann 2013).

10. Implications of SDV for evolution

Even if considered as a one-generation phenomenon only, SDV would have some evolutionary consequences. By providing a range of phenotypes from the same genotype, it enhances the chance to survive adverse conditions and to perpetuate evolution. However, the evolutionary relevance of SDV would be far greater if the underlying epigenetic signatures would be heritable, selectable, and evolvable under certain circumstances.

10.1 *Inheritance, reinforcement, and genetic solidification of SDV-induced epigenetic patterns*

The transgenerational inheritance of epigenetic patterns, either induced by SDV or environmental cues, is not yet generally accepted. This is in contrast to the mitotic inheritance of epigenetic signatures that ensures the establishment of morphologically and functionally diverse tissues and organs from the zygote (Ringrose and Paro 2007; Probst *et al.* 2009). The idea of transgenerational epigenetic inheritance and its role in evolution was first raised by Waddington (1942) and repeatedly reviewed in recent years (Jablonka and Raz 2009; Hauser *et al.* 2011; Pfennig and Servedio 2013). There are examples published for bacteria, plants, and animals (Henderson and Jacobsen 2007; Adam *et al.* 2008; Kovalchuk 2012), suggesting that this phenomenon is widespread and that its mechanisms may have been selected for during evolution (Jablonka 2012; Lim and Brunet 2013). The inherited state often shows incomplete penetrance, which means that only a proportion of the offspring is affected (Daxinger and Whitelaw 2012).

The transmission of epigenetic patterns to the next generation is quite plausible in bacteria and protists, which reproduce by binary fission. In plants, there is also great chance for epigenetic markers of soma cells to make their way into vegetative propagules or germ cells because plants often reproduce asexually and separate soma and germline late in development (Saze 2008). In animals, the situation is more complex. Following Weismann's germ plasm theory, mutations and epimutations of the soma cannot be transmitted to the germ cells and are therefore not heritable, as discussed in detail in Haig (2007) and

Jablonka and Raz (2009). However, this constraint was inferred from mammals and does not apply to all animal groups. In nematodes, insects, and vertebrates, there is indeed an early separation of the germline from the soma (Extavour and Akam 2003), but in sponges, cnidarians, bryozoans, flatworms, annelids, ascidians, and echinoderms, somatic cells can transform into germ cells in later life stages. Moreover, in these taxa, soma cells are also used to form new individuals by budding and fragmentation (De Meeûs *et al.* 2007; Schön *et al.* 2009), and thus, the transmission of epigenetic profiles to the next generation is easily understandable.

Sharma (2013) and Gapp *et al.* (2014) even raised the possibility of a soma-to-germline communication that might cause epigenetic modifications in the germ cells indirectly through modifications affecting primarily the soma. There is evidence for such a communication in plants and mouse by mobile regulatory RNAs and hormones. In animals, the accessibility of germ cells for blood-borne signals depends very much on taxon and the developmental stage of the gonads. For example, when the ovary is beginning to be formed in hatchlings of marbled crayfish the oogonia have direct contact to the haemolymph and are accessible for epimutagenic substances like the neighbouring tissues (figure 10A). The vitellogenic oocytes, in contrast, are separated from the haemolymph by follicle cells (figure 10B), which may keep such substances away.

In order to have long-term evolutionary consequences, epigenetic profiles generated by SDV and inherited to the next generation must be stabilized, reinforced, and eventually genetically solidified. Optimally, only those epigenetic patterns should be preserved and selected that accomplish adaptation to new environmental conditions not experienced by the parental generation (Hirsch *et al.* 2012). Herman *et al.* (2014) emphasized that the stability of epigenetic states beyond a single generation depends on the degree of environmental variation as well as on the costs of epigenetic resetting. Support for this view comes from Becker *et al.* (2011), who investigated spontaneous epimutations in 10 lineages of *Arabidopsis thaliana* over 30 generations under constant greenhouse conditions. They found that under these constant conditions, not many epimutations were stably inherited over the long term and that some sites seemed to go through recurrent cycles of forward and reverse epimutation.

Reinforcement of epigenetic profiles in new environments may be achieved by the interaction of SDV with phenotypic plasticity, the directional influence of environmental cues on epigenetic signatures (Scheiner 1993; Ghalambor *et al.* 2007). SDV and phenotypic plasticity are different epigenetic sources of phenotypic variation by definition but are coupled to some degree. SDV produces phenotypes *a priori* around a mean target phenotype, whereas phenotypic plasticity produces phenotypes *a posteriori* as the result of environmental cues, shifting the target phenotype to new optima. Both have in common that they can be mediated by DNA methylation. There is some more information on the mechanisms of coupling with respect to gene expression of yeast and bacteria. In yeast, coupling was found to be particularly strong for genes with specific promoter architecture (TATA box and high nucleosome occupancy) but weak for genes in which high noise may be detrimental (Lehner 2010). In *Escherichia coli*, coupling was influenced by the level of gene expression, dosage sensitivity of genes, and regulation by specific nucleoid-associated proteins and transcription factors (Singh 2013).

Zhang *et al.* (2013) established by glasshouse experiments that variation in DNA methylation can cause substantial heritable variation of ecologically important traits in *Arabidopsis thaliana* and concluded that epigenetic variation may speed up evolution. Cortijo *et al.* (2014) quantified the impact of heritable epigenetic variation on complex traits in isogenic *Arabidopsis* lines that carried experimentally induced DNA methylation changes at hundreds of regions across the genome. They demonstrated that several of these differentially methylated regions act as bona fide epigenetic quantitative trait loci, accounting for 60% to 90% of the heritability of flowering time and primary root length. These epigenetic quantitative trait loci can be subjected to artificial selection. Many of the experimentally induced differentially methylated regions also vary in natural *Arabidopsis* populations and may thus provide an epigenetic basis for Darwinian evolution.

The genetic solidification of epigenetically mediated phenotypes is often explained by genetic accomodation, genetic assimilation, and the Baldwin effect (Nanjundiah 2003; West-Eberhard 2003; Pigliucci *et al.* 2006; Crispo 2007; Angers *et al.* 2010). These mechanisms were proposed by West-Eberhard (2003), Waddington (1953), and Baldwin (1896), respectively, and explain how phenotypes originally produced in response to an environmental stimulus later become genetically encoded by artificial or natural selection. Genetic assimilation requires pre-existing genetic variability, whereas the Baldwin effect does not making it more suitable to explain genetic solidification of epigenetic variation in clonal populations (Nanjundiah 2003).

In the following, I would like to present three further ideas on the conversion of epigenetic variation into genetic variation, namely, facilitated genetic mutation in methylated DNA regions, activation of transposons by demethylation, and methylation dependent expression, duplication and elimination of copy number variants. Interestingly, methylated DNA regions have a 10- to 50-fold higher mutation rate than unmethylated regions, which might lead to targeted DNA sequence divergence. Methylated CpG sites can mutate to TpG and to CpA in the complementary strand (Elango *et al.* 2008; Hunt *et al.* 2010; Xia *et al.* 2012). In honeybee, genes

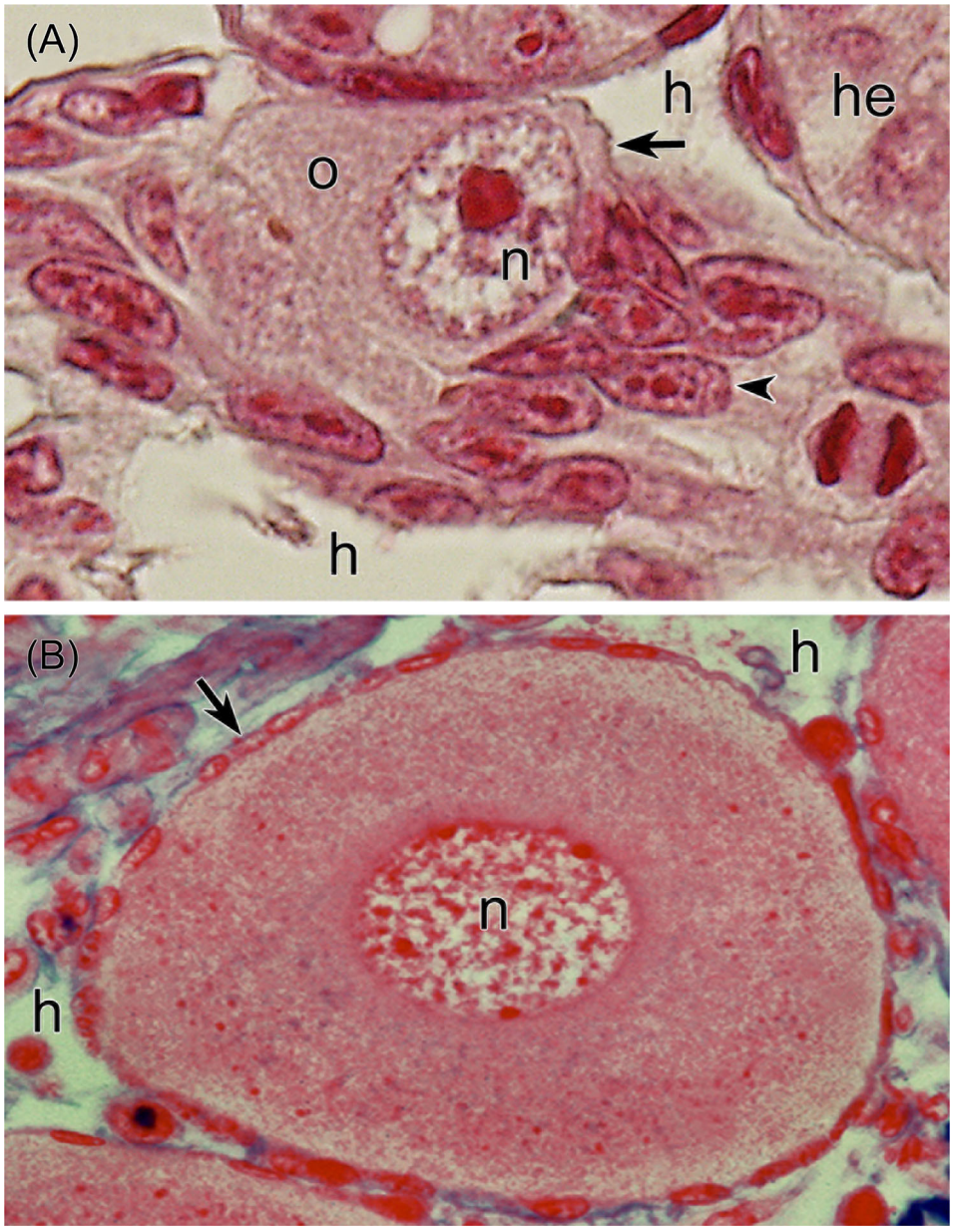

Figure 10. Accessibility of germ cells of marbled crayfish for epimutagenic signals. (**A**) Primordium of ovary in hatchling showing oogonium (o) with large nucleus (n) and surrounding matrix cells (arrowhead). The oogonium has direct contact (arrow) to the thoracic haemal sinus (h) and is thus equally accessible for blood-borne epimutagenic substances as the neighbouring hepatopancreas cells (he) (from Vogt 2015). (**B**) Vitellogenic oocyte being completely separated from the haemal sinuses by a capsule of follicle cells (arrow), which acts as a filter for blood-borne substances (from Vogt *et al.* 2004).

with high CpG content, i.e. higher probabilities of genetic mutation, are associated with developmental processes, whereas genes with low CpG content are associated with basic biological functions (Elango *et al.* 2008). Transposons are often silenced by DNA methylation. If activated by demethylation they can become powerful mutagens generating genetic diversity (Weigel and Colot 2012).

Gene duplication is recognized to play a fundamental role in the origin of phenotypic diversity and is sometimes regarded as a major evolutionary path towards the gain of new function and the origin of new species (Lynch and Conery 2000; Taylor and Raes 2004; Roth *et al.* 2007). Gene duplicates originate by errors in homologous recombination and by retrotransposition events and account for 8–20% of the genes in eukaryotic

genomes, with extremes of 90% in some plants (Moore and Purugganan 2005). The scenario in figure 11 starts from the DNA sequence of a parthenogenetic mother that includes slightly different copy number variants of a gene, one of them being active and the others being silenced by DNA methylation. In the next generation, the pattern of active and silenced duplicates is stochastically changed, resulting in genetically identical but epigenetically and phenotypically different batchmates. In the following generations and under the influence of different stabilizing environmental cues, long-term activated gene variants may be duplicated and some of the long-term silenced variants may be eliminated, resulting in lineages that differ from each other epigenetically and genetically. To date, there is no experimental evidence for such a mechanism but it is well known that genes duplicate quite often, that the activation status of copy number variants can change and that they can disappear from the genome (Rodin and Riggs 2003; Roth *et al.* 2007).

The sketched scenario of epigenetic diversification of a genetically uniform population and transformation of this epigenetic diversity into genetic diversity seems to be particularly important for the perpetuation and evolution of asexual lineages (Castonguay and Angers 2012; Verhoeven and Preite 2014). It may also be important for the radiation of small invasive groups in new environments (Dybdahl and Kane 2005; Ghalambor *et al.* 2007). The chance of the invasive generation to survive is certainly enhanced by the *a priori* provisioning of phenotypic variants via SDV. Differences in the preference of food, substrate, or temperature by the various phenotypes over generations may then generate diverse ecotypes, and genetic solidification of the epigenetic differences may finally lead to lineage splitting or even speciation.

10.2 *SDV as a novel evolution factor*

SDV can only be regarded as an evolution factor if at least some of its aspects are heritable, adaptable, selectable, and evolvable. All of these features have convincingly been demonstrated for stochastic gene expression in cultured bacteria and yeast (Ackermann 2013; Viney and Reece 2013). In multicellular organisms, the situation is more complex because some aspects of SDV may meet these requirements, for instance those mediated by DNA methylation, whereas others like those mediated by mechanical forces may not.

Viney and Reece (2013) presented evidence that phenotypic differences produced by stochastic gene expression in microorganisms can have fitness advantages suggesting that evolution can shape SDV. Fraser and Kærn (2009) discussed different scenarios where stochastic gene expression might bestow a selective advantage, highlighting a potential role of SDV for the evolution of microbial survival strategies. Based on empirical results and theoretical models, Zhang *et al.* (2009) suggested that for some yeast genes such as plasma-membrane transporters elevated levels of expression stochasticity are advantageous, are subject to positive selection, and facilitate the evolution of adaptive gene expression. Kaneko and Furusawa (2008) concluded from their work that growing cells have a general ability for adaptation by taking advantage of stochasticity in gene expression and emphasized its importance for the adaptation of microorganisms to different environments.

There is also evidence that selection can act on SDV-produced phenotypes in isogenic animal populations. Gärtner (1985, 1990) revealed SDV-caused Gaussian distributions for body weight in populations of inbred mice and rats and assumed that such distributions would be ideal for natural selection to act upon, resembling the Gaussian curves of sexually reproducing populations and the norm of reaction curves (Falconer and Mackay 1996; Schlichting and Pigliucci 1998). Experiments with inbred mice and rats in a selection-neutral laboratory environment indeed demonstrated the presence of sexual selection despite genetic uniformity. Males had the highest chance to parent the next generation when coming from the central classes around the mean body weight.

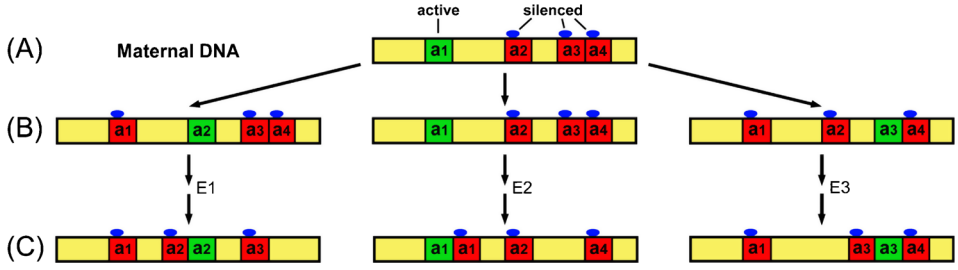

Figure 11. Hypothetical scenario on the transformation of epigenetic diversity into genetic diversity. (**A**) Starting point is a piece of DNA of a parthenogenetic female that includes four copy variants of a gene (a1–a4) with slightly different DNA sequences. Only one of these duplicates is active and three are silenced by DNA methylation. (**B**) The progeny are genetically identical with their mother and among each other but differ epigenetically due to stochastic activation and silencing of gene copies. (**C**) In the following generations the epigenetic patterns are stabilized under the influence of different environments (E1–E3). Finally, the epigenetic diversity is transformed into genetic diversity by the duplication of long-term active gene variants and the elimination of long-term silenced variants.

Evolvability is the capacity of a developmental system to adapt to selective pressures, which is largely a function of the system's ability to generate heritable phenotypic variation (Hendrikse *et al.* 2007). It has been convincingly demonstrated for stochastic gene expression in bacteria, yeast, and eukaryotic cell lines (Fraser *et al.* 2004; Kaneko and Furusawa 2008; Neildez-Nguyen *et al.* 2008; Viney and Reece 2013). In multicellular organisms, the various SDV generators and the buffering systems that limit them have genetic components as discussed earlier, and therefore, SDV should be evolvable in these organisms, too.

These examples apparently support the idea of SDV as an important, hitherto neglected evolution factor. It might add another interesting facet to the emerging *Extended Synthesis*, which attempts to integrate phenotype-based concepts and epigenetics into neo-Darwinian *Modern Synthesis* (Müller and Newman 2003; West-Eberhard 2003; Pigliucci and Müller 2010; Hallgrímsson and Hall 2011a; Jablonka and Lamb 2014).

10.3 *Evidence for an evolutionary role of SDV under natural conditions*

So far, I have reflected on evolutionary implications of SDV on the basis of laboratory experiments with clonal organisms. Evidence for the proposed evolutionary role of SDV in natural populations is weak, mainly because of the difficulty to distinguish between genetic, stochastic developmental, and environmental sources of phenotypic variation in the wild. However, there are some hints for the existence and effectiveness of SDV in nature coming from bet-hedging and social cooperation in environmental microorganisms, the radiation of obligatory parthenogenetic animal taxa, and the evolutionary success of bottlenecked and invasive populations.

SDV-related bet-hedging and social cooperation of microorganisms have been observed not only in the laboratory but also in nature. Using single-cell analysis, Yvert *et al.* (2013) profiled hundreds of quantitative traits in 37 natural strains of *Saccharomyces cerevisiae* from different geographical regions and ecological origin. They demonstrated trait specificity and quantitative differences between natural populations in 'phenotypic noise', supporting the possibility that microevolution might tune SDV in the wild. Nikel *et al.* (2014) concluded from their analysis of biodegradation of aromatic compounds in the saprotrophic soil bacterium *Pseudomonas putida* that SDV-related bet-hedging and social cooperation are important factors besides genetic mutation in pushing forward the evolution of environmental microorganisms. Further examples of SDV-related phenotypic differences in natural clonal lineages are summarized in Richard and Yvert (2014).

According to traditional belief, clonal lineages are dead ends of evolution because of the absence of genetic recombination, the most effective mechanism to create new phenotypes. Hence, higher taxa of obligate parthenogens should not exist. However, the bdelloid rotifers that lived without sex for about 40 million years as convincingly proven by Mark Welch and Meselson (2000) yielded 4 families, 18 genera, and 360 species. A similar diversity evolved in some obligate parthenogenetic freshwater ostracod groups, which exist since more than 100 million years without sex (Butlin *et al.* 1998). The diversity of such evolutionarily successful asexuals is usually explained with random mutation, the temporal appearance of sexually reproducing individuals, the separate origins of clones from sexual ancestors, and hybridization between asexual females and males from related sexual species, but all of these arguments are purely hypothetical. An alternative explanation might be clonal splitting by the interaction of SDV, phenotypic plasticity, epigenetic inheritance, and genetic solidification as outlined above.

Another hint for the effectiveness of SDV in the wild comes from the evolutionary success of genetically bottlenecked populations and small invasive groups. SDV may help to survive the bottleneck and the invasive period, facilitating further evolution. A good example for an evolutionary very successful bottlenecked species is modern humans, which went through one or more bottlenecks of a few thousand individuals in the Pleistocene (Ambrose 1998) but have yielded a broad range of phenotypically different ethnicities since then. The effectiveness of SDV in biological invasions may be best illustrated by the marbled crayfish of Madagascar. In about 2005, somebody released one or a few individuals of this crayfish near the capital of Madagascar. Thereafter, this exotic multiplied in an enormous speed and invaded habitats diverse as rice paddies, rivers, lakes, and swamps in eight of the country's 22 regions (Jones *et al.* 2009). SDV has probably facilitated survival of the first generation and the establishment of founder populations in the different habitats.

10.4 *Origin of SDV and relative importance in different evolutionary periods*

There are essentially three chance generators that produce phenotypic variants without knowing the future conditions, namely random mutation, meiotic recombination, and SDV. Random mutation is thought to date back to the beginning of life, whereas meiotic recombination originated much later in context with sexual reproduction. SDV evolved at different times, depending on specification. Due to its occurrence in all kingdoms of life, inter-individual SDV probably dates back to the first cellular organisms that appeared some 3.5 billion years ago (Cavalier-Smith 2006) or even to a possibly preceding

virus world (Koonin *et al.* 2006). Fluctuating asymmetry and variation among homonomous metamers emerged much later in the context of multicellularity. Variation among homonomous metamers evolved in algae, animals, and vascular plants some 1200, 530, and 430 million years ago, respectively (Kenrick and Crane 1997; Butterfield 2000; Couso 2009). Fluctuating asymmetry appeared together with bilateral symmetry at about 600 Mya in animals and 430 Mya in vascular plants (Finnerty *et al.* 2004).

The relative importance of random mutation, meiotic recombination, and SDV for the *a priori* production of phenotypic variants has supposedly changed during evolution depending on cell and body architecture, mode of reproduction, and life histories of the prevailing taxa. In the first 1.7 billion years of life, organisms were exclusively prokaryotic and reproduced asexually. Prokaryotes are thought to generate phenotypic variation mainly by random mutation and to a lesser degree by recombination and horizontal gene transfer (Denamur and Matic 2006; Lawrence and Retchless 2009). The involvement of SDV in this process has been recognized in recent years in connection with stochastic gene expression, but its share in the *a priori* generation of phenotypic variation in prokaryotes is not yet established.

The eukaryotic cells appeared on the scene at about 1800 Mya. The first eukaryotes were asexually reproducing protists (Knoll *et al.* 2006). Most of the extant protists still reproduce asexually with rare interspersed sex (Dacks and Roger 1999). For instance, in the ichthyosporean *Pseudoperkinsus tapetus*, 1 sexual cycle for every 22,700 asexual cycles was determined (Marshall and Berbee 2010). The origin of sexual reproduction and concomitant meiotic recombination is obscure. It is dated to between 1700 and 850 Mya (Zhu and Chen 1995; Cavalier-Smith 2010). The predominance of asexual reproduction and the considerable augmentation of stochasticity generating mechanisms in protists compared to bacteria suggest that the relative importance of SDV may have increased in the 'age of the protists'.

Sexual reproduction is the rule in multicellular animals and plants, which dominate the picture of modern ecosystems (Bell 1982). Therefore, the relevance of meiotic recombination in the production of phenotypic diversity is assumed to have dramatically increased since the Cambrian radiation of the Animalia and the conquest of land by the vascular plants. The relative role of SDV has probably decreased in this time period despite the emergence of new stochasticity generators. However, for all asexually reproducing taxa and genetically impoverished populations SDV is still of prime importance.

11. Problems, open questions, and some future research directions

Among animal biologists, there is no consensus on whether SDV is real or just an experimental artefact as discussed in Larsen (2005) and Oey and Whitelaw (2012). Cell biologists and microbiologists are one step ahead because at least stochastic gene expression is widely accepted. The arguments made against SDV in animals mainly result from the difficulty to demarcate it from the genetic and environmental proportions of phenotypic variation. The indoor experiments with isogenic animals reviewed in this article strongly suggest that SDV is real and a source of phenotypic variation in its own right. The most impressive examples of the impact of SDV on phenotype are spotted coat coloration and wiring of the brain. It seems inherently unlikely that the pigmentation of each of the billions of hair follicles in cattle is determined by a specific genetic instruction (Seidel *et al.* 2003) and that the human brain with its 10^{15} synapses is genetically specified down to the finest detail (Clarke 2012).

Theoretically, SDV is the phenotypic variation that remains after subtraction of genetic variation and environmental variation from total phenotypic variation. In reality, however, measured SDV may be curtailed to some degree by individual genetic mutations and non-shared micro-environmental influences. These factors largely elude detection and measurement and are therefore often urged as arguments against SDV. Genetic differences of clonemates can come from mutations in the germline of the parent or from somatic mutations in the clonemates. Recent whole-genome sequencing revealed random mutation values per haploid genome per generation of 0.001, 0.99, 2.9 and 87.5 in *Escherichia coli*, *Drosophila melanogaster*, *Caenorhabditis elegans* and *Homo sapiens*, respectively (Lynch *et al.* 2008; The 1000 Genomes Project Consortium 2010; Lee *et al.* 2012), suggesting that germline mutations do not markedly contibute to phenotypic diversity of the offspring.

The potential of somatic mutations for curtailing putative SDV is much dependent on the number of soma cells in an organism and the corresponding frequency of cell division (Favor and Neuhäuser-Klaus 1994; Gill *et al.* 1995). In the nematode *Caenorhabditis elegans*, in which 1090 cells form the adult body, somatic mutations are largely irrelevant. Humans, in contrast, have approximately 10^{13} to 10^{14} cells and a correspondingly higher frequency of cell division suggesting that most human cells carry at least one spontaneous mutation (Frank 2010). Comparison of the whole genome of blood cells between human monozygotic twins indeed revealed differences in single nucleotide polymorphisms and copy-number variants (Bruder *et al*. 2008; Maiti *et al*. 2011), demonstrating that organisms regarded as genetically identical display some genetic differences, indeed. Therefore, in long-lived organisms with large body sizes like cattle and humans, somatic mutations may curtail SDV to some degree (Biesecker and Spinner 2013).

Micro-environmental influences like local differences in light and temperature are certainly relevant for populations in the wild, particularly for plants and sessile animals.

However, in simple laboratory settings like those used for the culture of *Caenorhabditis*, *Drosophila*, *Daphnia*, marbled crayfish, and mice and rats, such influences can be reduced to almost zero. Larger mammals like pigs and cattle require higher diversification of facilities and food, leaving more room for speculations on the curtailing effect of non-shared environment on SDV. This holds even more for human monozygotic twins. In mammals, micro-environmental parameters of the uterus were sometimes assumed to considerably influence phenotypic variation of twins. However, transplantation experiments with artificially prepared calf twins revealed that the uterine environment contributes only a few percent to the variation of size and body weight in later life (Gärtner *et al.* 1991).

There are still many open questions on SDV, which require more intense investigation, particularly with respect to animals and plants. Among them are the mediation of SDV by molecular epigenetic mechanisms, the relationship between SDV and phenotypic plasticity in natural environments, the transgenerational inheritance of epigenetic patterns, the conversion of epigenetic differences into genetic differences, and the experimental manipulation of SDV. The availability of SDV-models with different features and the application of modern genomic, epigenomic and postgenomic techniques may help to answer these questions.

The concept of transgenerational epigenetic inheritance is of fundamental importance to understand how epigenetic signatures spread across generations, no matter whether they mediate SDV or phenotypic plasticity (Lim and Brunet 2013; Pfennig and Servedio 2013). Although there are some good examples from different organisms, this type of information transfer is not yet generally accepted. A major problem is that most experiments were run over 2 to 3 generations only. Further research is needed to clarify, how and under what conditions epigenetic marks are inherited and under what conditions they persist. These questions are presently under investigation in several laboratories (Ashe *et al.* 2012; Skinner *et al.* 2012; Turck and Coupland 2014). The genetic solidification of epigenetically mediated phenotypic differences is even more contentious. Although it would make rapid evolutionary changes more plausible, it remains to be elucidated if mechanisms like genetic assimilation or the Baldwin effect really exist, how they act, and how often they are involved in evolutionary change (Braendle and Flatt 2006; Schlichting and Wund 2014).

The proposed scenario on lineage splitting and speciation by the interaction of SDV, transgenerational epigenetic inheritance, phenotypic plasticity, and genetic solidification of epigenetic differences could principally be proven by exposing genetically identical but phenotypically different cohorts of batchmates to strikingly different environments and monitoring sensitive epigenetic and genetic markers over many generations. Alternatively, one could compare the genomes and epigenomes of populations from different natural habitats that are known to have evolved from a single introduced clone. A good example is the marbled crayfish of Madagascar, which has generated different ecotypes from a single clone within 10 years (Jones *et al.* 2009). Another interesting example is the obligatory parthenogenetic American clone of *Daphnia pulex* that was introduced into Lake Naivasha (Kenya) in 1927. This clone has completely displaced native *Daphnia pulex* from Ethiopia to South Africa (Mergeay *et al.* 2006). Interestingly, it would not only allow comparison of epigenetic and genetic markers of populations from different habitats but also of earlier generations that have left behind dormant eggs in subsequent sediment layers.

One of the reasons for the low interest of researchers in SDV may result from its chance character that apparently prohibits forecasting and manipulation. However, at least some aspects of SDV can be manipulated, for instance, by influencing the buffering system via Hsp90 and microRNAs (Li *et al.* 2010; Kim and Sauro 2012). Another promising approach to modify SDV is drug interference with molecular epigenetic mediators like DNA methylation and histone acetylation (Ho *et al.* 2013; Fischer 2014).

Numerous authors have written on SDV before me and some of them have presented profound arguments on its biological relevance. In this article, I have summarized these works, added my own experimental data and ideas, and endeavoured to conceptualize SDV across all kingdoms of life and major fields of biology. Of course, this review is not the final truth. Rather, it is hoped to provide a framework for fruitful discussions among experts and help to design future experiments that are more target-oriented. Further refinement of this SDV-concept requires the input of colleagues from various experimental and theoretical biological disciplines. It was beyond the scope of this article to intensely discuss the consequences of SDV for human life, but psychologists and social scientists may pick up the ball.

12. Conclusions

(1) Experiments with genetically identical organisms in highly standardized laboratory environments clearly revealed that there is a third source of phenotypic variation besides genetic variation and environmental variation, namely, stochastic developmental variation. Although known for more than a century, this source of phenotypic variation has not made its way into biological theory, probably because of its unpredictable character and the difficulty to demarcate it from genetic and environmental variation in the wild. Meanwhile, there are several suitable model organisms available to investigate SDV in detail.

(2) Studies on organisms diverse as archaeans, bacteria, protists, fungi, plants, and animals suggest that SDV is a universal and phylogenetically old principle, which serves for the *a priori* production of phenotypic variants around a well-adapted target phenotype. There are considerable differences in SDV generation among the supergroups of life depending on cell architecture, body plan, and life style.

(3) SDV can be produced at all levels of biological organization from molecule to organism. It results from stochastic cellular processes, nonlinear chemical and mechanical mechanisms of patterning and organogenesis, and probabilistic self-reinforcing circuitries in the adult life. It is mediated by molecular epigenetic mechanisms like DNA methylation and higher-level epigenetic mechanisms like self-organization within developing tissues.

(4) SDV was shown to vary considerably among traits and trait categories. In animals, it is mostly relatively small for morphometric characters, larger for biochemical and physiological traits and largest for behavioural and life history traits. Some characters like fingerprints and spotted coloration of the integument have an extremely broad range of SDV. Inter-individual SDV and intra-individual fluctuating asymmetry are different outcomes of developmental stochasticity and are not narrowly correlated.

(5) It is commonly believed that in a particular environment a single DNA-sequence and its copies map to one phenotype only. However, thanks to SDV, genotype-to-phenotype mapping is one to many even under this condition generating individuality in clonal populations. This individualizing effect of SDV curtails the dream of producing organisms with identical properties for human benefit by inbreeding or artificial cloning.

(6) SDV has been feared for long as an obstacle in the standardization of test animals and breeding of true-to-type plants. On the other side, SDV could be exploited for the improvement of crop and microbial strains for biotechnology. In medicine, SDV receives increasing attention as a modifier of the infectivity and resistance of pathogens, which are mostly asexual organisms. There are first ideas on how to manipulate the dimensions of SDV, either to reduce its nuisance effects or to enhance its beneficial properties.

(7) The production of different phenotypes from the same genotype by SDV is a bet-hedging strategy that enhances the chance to stay in the game of life when the environmental conditions change. This strategy is particularly advantageous for clonal and genetically impoverished populations. Further ecological implications of SDV include epigenetic chance generation in populations, the production of functional biodiversity, and facilitation of social interaction in clonal groups.

(8) There is no long-term experimental proof yet for SDV as an evolution factor. However, it seems plausible that phenotypes produced by SDV can serve as raw material for natural selection. The underlying epigenetic patterns may be inherited under certain conditions, reinforced by environmental cues, and genetically solidified, yielding different ecotypes or even species on the long term. Some aspects of SDV such as stochastic gene expression have been shown to be heritable, adaptable, selectable, and evolvable, supporting the idea of SDV as a hitherto overlooked evolution factor.

(9) SDV affects almost all aspects of life, either negatively as a nuisance or positively as a bet-hedging strategy, and therefore, it requires a higher level of attention and more adequate integration into biological theory. The current attempt to conceptualize SDV across the entire spectrum of organisms and trait categories is intended to stimulate discussion among experts from various disciplines in order to achieve this goal.

Acknowledgements

The author is grateful to the following colleagues for providing pictures and information: Martin Ackermann (Zurich), Gregory S Archer (Davis), Gregory A Babitt (Rochester), Jürgen Berger and Ralf J Sommer (Tübingen), Brian Bagatto (Akron), John Daugman (Cambridge), Jan Dijksterhuis and Han Wösten (Utrecht), David Fenwick (Penzance), Theodore H Friend (College Station), Mikael Häggström (Uppsala), David S Haskell (Sewanee), John F Hasler (Bogart), Anil K Jain (East Lansing), Nikos C Kyrpides (Walnut Creek), Winfried Lampert (Plön), Eric C Lai (New York), David IK Martin (Oakland), Erskine L Palmer and Russell Regnery (Atlanta), Soo-Bong Park (Suwon), Jorge A Piedrahita (Raleigh), Pascal Radtke (Düsseldorf), George E Seidel Jr (Fort Collins), Michael R Strand (Athens), Stefano Tiozzo (Villefranche-sur-Mer), Rogier R van Vugt (Leiden), Larry Wadsworth and Mark Westhusin (College Station), and Alex Wild (Champaign-Urbana). Many thanks also to Vidyanand Nanjundiah (Bangalore) and an anonymous referee for constructive criticism and numerous suggestions that helped to improve the manuscript.

References

Acar M, Mettetal JT and van Oudenaarden A 2008 Stochastic switching as a survival strategy in fluctuating environments. *Nat. Genet.* **40** 471–475

Ackermann M 2013 Microbial individuality in the natural environment. *ISME J.* **7** 465–467

Ackermann H-W and Smirnoff WA 1983 A morphological investigation of 23 baculoviruses. *J. Invertebr. Pathol.* **41** 269–280

Ackermann M, Stecher B, Freed NE, Songhet P, Hardt W-D and Doebeli M 2008 Self-destructive cooperation mediated by phenotypic noise. *Nature* **454** 987–990

Adam M, Murali B, Glenn NO and Potter SS 2008 Epigenetic inheritance based evolution of antibiotic resistance in bacteria. *BMC Evol. Biol.* **8** 52

Adelman DE 2005 The false promise of the genomics revolution for environmental law. *Harv. Environ. Law Rev.* **29** 117–178

Adl SM, Simpson AGB, Lane CE, Lukeš J, Bass D, *et al.* 2012 The revised classification of eukaryotes. *J. Eukaryot. Microbiol.* **59** 429–493

Ahluwalia JK, Hariharan M, Bargaje R, Pillai B and Brahmachari V 2009 Incomplete penetrance and variable expressivity: is there a microRNA connection? *BioEssays* **31** 981–992

Alwes F and Scholtz G 2006 Stages and other aspects of the embryology of the parthenogenetic Marmorkrebs (Decapoda, Reptantia, Astacida). *Dev. Genes Evol.* **216** 169–184

Ambrose SH 1998 Late Pleistocene human population bottlenecks, volcanic winter, and differentiation of modern humans. *J. Hum. Evol.* **34** 623–651

Angers B, Castonguay E and Massicotte R 2010 Environmentally induced phenotypes and DNA methylation: how to deal with unpredictable conditions until the next generation and after. *Mol. Ecol.* **19** 1283–1295

Aranda-Anzaldo A and Dent MAR 2003 Developmental noise, ageing and cancer. *Mech. Ageing Dev.* **124** 711–720

Archer GS, Dindot S, Friend TH, Walker S, Zaunbrecher G, Lawhorn B and Piedrahita JA 2003a Hierarchical phenotypic and epigenetic variation in cloned swine. *Biol. Reprod.* **69** 430–436

Archer GS, Friend TH, Piedrahita J, Nevill CH and Walker S 2003b Behavioral variation among cloned pigs. *Appl. Anim. Behav. Sci.* **82** 151–161

Arias AM and Hayward P 2005 Filtering transcriptional noise during development: concepts and mechanisms. *Nat. Rev. Genet.* **7** 34–44

Ariew A and Lewontin RC 2004 The confusions of fitness. *Brit. J. Phil. Sci.* **55** 347–363

Ashe A, Sapetschnig A, Weick E-M, Mitchell J, Bagijn MP, Cording AC, Doebley A-L, Goldstein LD, *et al*. 2012 piRNAs can trigger a multigenerational epigenetic memory in the germline of *C. elegans*. *Cell* **150** 88–99

Astauroff BL 1930 Analyse der erblichen Störungsfälle der bilateralen Symmetrie im Zusammenhang mit der selbständigen Variabilität ähnlicher Strukturen. *Z. indukt. Abst. Vererbungsl.* **55** 183–262

Avendaño MS, Leidy C and Pedraza JM 2013 Tuning the range and stability of multiple phenotypic states with coupled positive-negative feedback loops. *Nat. Commun.* **4** 2605

Avery SV 2006 Microbial cell individuality and the underlying sources of heterogeneity. *Nat. Rev. Microbiol.* **4** 577–587

Avise JC 2008 *Clonality: the genetics, ecology, and evolution of sexual abstinence in vertebrate animals* (New York: Oxford University Press)

Babbitt GA 2008 How accurate is the phenotype? – An analysis of developmental noise in a cotton aphid clone. *BMC Dev. Biol.* **8** 19

Bailey DW 1982 How pure are inbred strains of mice? *Immunol. Today* **3** 210–214

Bairu MW, Aremu AO and van Staden J 2011 Somaclonal variation in plants: causes and detection methods. *Plant Growth Regul.* **63** 147–173

Balaban NQ 2011 Persistence: mechanisms for triggering and enhancing phenotypic variability. *Curr. Opin. Genet. Dev.* **21** 768–775

Balázsi G, van Oudenaarden A and Collins JJ 2011 Cellular decision-making and biological noise: from microbes to mammals. *Cell* **144** 910–925

Baldwin JM 1896 A new factor in evolution. *Am. Nat.* **30** 441–451

Bartel DP and Chen C-Z 2004 Micromanagers of gene expression: the potentially widespread influence of metazoan microRNAs. *Nat. Rev. Genet.* **5** 396–400

Barthélémy D and Caraglio Y 2007 Plant architecture: a dynamic, multilevel and comprehensive approach to plant form, structure and ontogeny. *Ann. Bot.* **99** 375–407

Barton NH and Charlesworth B 1998 Why sex and recombination? *Science* **281** 1986–1990

Batada NN and Hurst LD 2007 Evolution of chromosome organization driven by selection for reduced gene expression noise. *Nat. Genet.* **39** 945–949

Beatty J 2006 Chance variation: Darwin on orchids. *Philos. Sci.* **73** 629–641

Beatty J 2010 Reconsidering the importance of chance variation; in *Evolution: the extended synthesis* (eds) M Pigliucci and GB Müller (Cambridge: MIT Press) pp 21–44

Beaumont HJE, Gallie J, Kost C, Ferguson GC and Rainey PB 2009 Experimental evolution of bet hedging. *Nature* **462** 90–93

Beck JA, Lloyd S, Hafezparast M, Lennon-Pierce M, Eppig JT, Festing MFW and Fisher EMC 2000 Genealogies of mouse inbred strains. *Nat. Genet.* **24** 23–25

Becker C, Hagmann J, Müller J, Koenig D, Stegle O, Borgwardt K and Weigel D 2011 Spontaneous epigenetic variation in the *Arabidopsis thaliana* methylome. *Nature* **480** 245–249

Bell G 1982 *The masterpiece of nature: the evolution and genetics of sexuality* (London: Croom Helm)

Bell AM 2007 Animal personalities. *Nature* **447** 539–540

Ben-Ami F and Hodgson AN 2005 Ovoviviparity and the structure of the brood pouch in *Melanoides tuberculata* (Gastropoda: Prosobranchia: Thiaridae). *J. Morphol.* **263** 322–329

Benzer S 1953 Induced synthesis of enzymes in bacteria analyzed at the cellular level. *Biochim. Biophys. Acta* **11** 383–395

Biesecker LG and Spinner NB 2013 A genomic view of mosaicism and human disease. *Nat. Rev. Genet.* **14** 307–320

Bigger JW 1944 Treatment of staphylococcal infections with penicillin by intermittent sterilisation. *Lancet* **244** 497–500

Bird A 2002 DNA methylation patterns and epigenetic memory. *Genes Dev.* **16** 6–21

Boettiger AN and Levine M 2009 Synchronous and stochastic patterns of gene activation in the *Drosophila* embryo. *Science* **325** 471–473

Bolger DT and Case TJ 1992 Intra- and interspecific interference behaviour among sexual and asexual geckos. *Anim. Behav.* **44** 21–30

Bosl WJ and Li R 2010 The role of noise and positive feedback in the onset of autosomal dominant diseases. *BMC Syst. Biol.* **4** 93

Bossdorf O, Arcuri D, Richards CL and Pigliucci M 2010 Experimental alteration of DNA methylation affects the phenotypic plasticity of ecologically relevant traits in *Arabidopsis thaliana*. *Evol. Ecol.* **24** 541–553

Braendle C and Flatt T 2006 A role for genetic accommodation in evolution? *BioEssays* **28** 868–873

Breithaupt T and Eger P 2002 Urine makes the difference: chemical communication in fighting crayfish made visible. *J. Exp. Biol.* **205** 1221–1232

Breuker CJ, Patterson JS and Klingenberg CP 2006 A single basis for developmental buffering of *Drosophila* wing shape. *PLoS ONE* **1** e7

Brock DW 2002 Human cloning and our sense of self. *Science* **296** 314–316

Brown CR, Mao C, Falkovskaia E, Jurica MS and Boeger H 2013 Linking stochastic fluctuations in chromatin structure and gene expression. *PLoS Biol.* **11** e1001621

Browne RA, Moller V, Forbes VE and Depledge MH 2002 Estimating genetic and environmental components of variance using sexual and clonal *Artemia*. *J. Exp. Mar. Biol. Ecol.* **267** 107–119

Bruder CEG, Piotrowski A, Gijsbers AACJ, Andersson R, Erickson S, *et al*. 2008 Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. *Am. J. Hum. Genet.* **82** 763–771

Buss LW 1987 *The evolution of individuality* (Princeton: Princeton University Press)

Butlin R, Schön I and Martens K 1998 Asexual reproduction in nonmarine ostracods. *Heredity* **81** 473–480

Butterfield NJ 2000 *Bangiomorpha pubescens* n. gen., n. sp.: implications for the evolution of sex, multicellularity, and the Mesoproterozoic/Neoproterozoic radiation of eukaryotes. *Paleobiol.* **26** 386–404

Caballero L, Benítez M, Alvarez-Buylla ER, Hernández S, Arzola AV and Cocho G 2012 An epigenetic model for pigment patterning based on mechanical and cellular interactions. *J. Exp. Zool. (Mol. Dev. Evol.)* **318** 209–223

Calo S, Billmyre RB and Heitman J 2013 Generators of phenotypic diversity in the evolution of pathogenic microorganisms. *PLoS Pathog.* **9** e1003181

Canli T (ed) 2006 *Biology of personality and individual differences* (New York: Guilford Press)

Casadesús J and Low DA 2013 Programmed heterogeneity: epigenetic mechanisms in bacteria. *J. Biol. Chem.* **288** 13929–13935

Case TJ 1990 Patterns of coexistence in sexual and asexual species of *Cnemidophorus* lizards. *Oecologia* **83** 220–227

Castonguay E and Angers B 2012 The key role of epigenetics in the persistence of asexual lineages. *Genet. Res. Int.* **2012** 534289

Cavalier-Smith T 2006 Cell evolution and Earth history: stasis and revolution. *Phil. Trans. R. Soc. B* **361** 969–1006

Cavalier-Smith T 2010 Deep phylogeny, ancestral groups and the four ages of life. *Phil. Trans. R. Soc. B* **365** 111–132

Chan IS and Ginsburg GS 2011 Personalized medicine: progress and promise. *Annu. Rev. Genomics Hum. Genet.* **12** 217–244

Chang HH, Hemberg M, Barahona M, Ingber DE and Huang S 2008 Transcriptome-wide noise controls lineage choice in mammalian progenitor cells. *Nature* **453** 544–548

Charlesworth B and Charlesworth D 2010 *Elements of evolutionary genetics* (Greenwood Village: Roberts and Company Publishers)

Chase HB 1939 Studies on the tricolor pattern of the Guinea pig. I. The relations between different areas of the coat in respect to the presence of color. *Genetics* **24** 610–621

Chen Z-X and Riggs AD 2011 DNA methylation and demethylation in mammals. *J. Biol. Chem.* **286** 18347–18353

Childs DZ, Metcalf CJE and Rees M 2010 Evolutionary bet-hedging in the real world: empirical evidence and challenges revealed by plants. *Proc. R. Soc. B* **277** 3055–3064

Clarke PGH 2012 The limits of brain determinacy. *Proc. R. Soc. B* **279** 1665–1674

Cohn M and Horibata K 1959 Analysis of the differentiation and of the heterogeneity within a population of *Escherichia coli* undergoing induced ß-galactosidase synthesis. *J. Bacteriol.* **78** 613–623

Cornish-Bowden A and Nanjundiah V 2006 The basis of dominance; in *The biology of genetic dominance* (ed) RA Veitia (Georgetown: Landes Bioscience) pp 1–16

Cortijo S, Wardenaar R, Colomé-Tatché M, Gilly A, Etcheverry M, Labadie K, Caillieux E, Hospital F, *et al*. 2014 Mapping the epigenetic basis of complex traits. *Science* **343** 1145–1148

Couso JP 2009 Segmentation, metamerism and the Cambrian explosion. *Int. J. Dev. Biol.* **53** 1305–1316

Crispo E 2007 The Baldwin effect and genetic assimilation: revisiting two mechanisms of evolutionary change mediated by phenotypic plasticity. *Evolution* **61** 2469–2479

Cropley JE, Suter CM, Beckman KB and Martin DIK 2010 CpG methylation of a silent controlling element in the murine A^{vy}allele is incomplete and unresponsive to methyl donor supplementation. *PLoS ONE* **5** e9055

Czyz W, Morahan JM, Ebers GC and Ramagopalan SV 2012 Genetic, environmental and stochastic factors in monozygotic twin discordance with a focus on epigenetic differences. *BMC Med.* **10** 93

Dacks J and Roger AJ 1999 The first sexual lineage and the relevance of facultative sex. *J. Mol. Evol.* **48** 779–783

Daugman J and Downing C 2001 Epigenetic randomness, complexity and singularity of human iris patterns. *Proc. R. Soc. B* **268** 1737–1740

Davey Smith G 2011 Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice. *Int. J. Epidemiol.* **40** 537–562

Davidson RJ 2001 Towards a biology of personality and emotion. *Ann. N.Y. Acad. Sci.* **935** 191–207

Davidson CJ and Surette MG 2008 Individuality in bacteria. *Annu. Rev. Genet.* **42** 253–268

Davis MA 2009 *Invasion biology* (Oxford: Oxford University Press)

Dawson NJ 1970 Body composition of inbred mice (*Mus musculus*). *Comp. Biochem. Physiol.* **37** 589–593

Daxinger L and Whitelaw E 2012 Understanding transgenerational epigenetic inheritance via the gametes in mammals. *Nat. Rev. Genet.* **13** 153–162

Dayel MJ, Alegado RA, Fairclough SR, Levin TC, Nichols SA, McDonald K and King N 2011 Cell differentiation and morphogenesis in the colony-forming choanoflagellate *Salpingoeca rosetta*. *Dev. Biol.* **357** 73–82

Debat V and David P 2001 Mapping phenotypes: canalization, plasticity and developmental stability. *Trends Ecol. Evol.* **16** 555–561

Debat V and Peronnet F 2013 Asymmetric flies: the control of developmental noise in *Drosophila*. *Fly* **7** 70–77

Debat V, Alibert P, David P, Paradis E and Auffray J-C 2000 Independence between developmental stability and canalization in the skull of the house mouse. *Proc. R. Soc. B* **267** 423–430

De Kroon H and van Groenendael J (eds) 1997 *The ecology and evolution of clonal plants* (Leiden: Backhuys Press)

Delbrück M 1945 The burst size distribution in the growth of bacterial viruses (bacteriophages). *J. Bacteriol.* **50** 131–135

Delvigne F and Goffin P 2014 Microbial heterogeneity affects bioprocess robustness: dynamic single-cell analysis contributes to understanding of microbial populations. *Biotechnol. J.* **9** 61–72

De Meeûs T, Prugnolle F and Agnew P 2007 Asexual reproduction: genetics and evolutionary aspects. *Cell. Mol. Life Sci.* **64** 1355–1372

De Meeûs T, Prugnolle F and Agnew P 2009 Asexual reproduction in infectious diseases; in *Lost sex. The evolutionary biology of parthenogenesis* (eds) I Schön, K Martens and P van Dijk (Dordrecht: Springer) pp 517–533

Denamur E and Matic I 2006 Evolution of mutation rates in bacteria. *Mol. Microbiol.* **60** 820–827

De Schepper S, Debergh P, van Bockstaele E, de Loose M, Gerats A and Depicker A 2003 Genetic and epigenetic aspects of somaclonal variation: flower colour bud sports in azalea, a case study. *South African J. Bot.* **69** 117–128

Dhar N and McKinney JD 2007 Microbial phenotypic heterogeneity and antibiotic tolerance. *Curr. Opin. Microbiol.* **10** 30–38

Dietrich J-E and Hiiragi T 2007 Stochastic patterning in the mouse pre-implantation embryo. *Development* **134** 4219–4231

Dijksterhuis J and Wösten H (eds) 2013 Development of *Aspergillus niger*. Studies in Mycology 74 (Utrecht: CBS-KNAW Fungal Biodiversity Centre)

Dohle W, Gerberding M, Hejnol A and Scholtz G 2004 Cell lineage, segment differentiation, and gene expression in crustaceans; in *Evolutionary developmental biology of Crustacea* (ed) G Scholtz (Lisse: Balkema) pp 95–133

Dos Santos RV and da Silva LM 2013 The noise and the KISS in the cancer stem cells niche. *J. Theoret. Biol.* **335** 79–87

Dybdahl MF and Kane SL 2005 Adaptation vs. phenotypic plasticity in the success of a clonal invader. *Ecology* **86** 1592–1601

Eckert CG 2002 The loss of sex in clonal plants. *Evol. Ecol.* **15** 501–520

Elango N, Kim S-H, NISC Comparative Sequencing Program, Vigoda E and Yi SV 2008 Mutations of different molecular origins exhibit contrasting patterns of regional substitution rate variation. *PLoS Comput. Biol* **4** e1000015

Eldar A and Elowitz MB 2010 Functional roles for noise in genetic circuits. *Nature* **467** 167–173

Elliott D 1998 Uniqueness, individuality, and human cloning. *J. Appl. Philos.* **15** 217–230

Elowitz MB, Levine AJ, Siggia ED and Swain PS 2002 Stochastic gene expression in a single cell. *Science* **297** 1183–1186

Extavour CG and Akam M 2003 Mechanisms of germ cell specification across the metazoans: epigenesis and preformation. *Development* **130** 5869–5884

Falconer DS and Mackay TFC 1996 *Introduction to quantitative genetics,* 4th ed. (Harlow: Longman)

Farca Luna AJ, Hurtado-Zavala JI, Reischig T and Heinrich R 2009 Circadian regulation of agonistic behavior in groups of parthenogenetic marbled crayfish, *Procambarus sp. J. Biol. Rhythms* **24** 64–72

Favor J and Neuhäuser-Klaus A 1994 Genetic mosaicism in the house mouse. *Annu. Rev. Genet.* **28** 27–47

Feinberg AP and Irizarry RA 2010 Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. *PNAS* **107** 1757–1764

Field LM and Blackman RL 2003 Insecticide resistance in the aphid *Myzus persicae* (Sulzer): chromosome location and epigenetic effects on esterase gene expression in clonal lineages. *Biol. J. Linn. Soc.* **79** 107–113

Figueiredo LM, Cross GAM and Janzen CJ 2009 Epigenetic regulation in African trypanosomes: a new kid on the block. *Nat. Rev. Microbiol.* **7** 504–513

Finch CE and Kirkwood TBL 2000 *Chance, development, and aging* (New York: Oxford University Press)

Finnerty JR, Pang K, Burton P, Paulson D and Martindale MQ 2004 Origins of bilateral symmetry: *Hox* and *Dpp* expression in a sea anemone. *Science* **304** 1335–1337

Fischer A 2014 Epigenetic memory: the Lamarckian brain. *EMBO J.* **33** 945–967

Flamme A 1977 *Untersuchungen über die Ursachen der phänotypischen Varianz quantitativer Merkmale bei Laboratoriumsratten.* Doktorarbeit (Hannover: Technische Universität Hannover)

Forde BG 2009 Is it good noise? The role of developmental instability in the shaping of a root system. *J. Exp. Bot.* **60** 3989–4002

Fox Keller E 2010 *The mirage of a space between nature and nurture* (Durham: Duke University Press)

Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suñer D, Cigudosa JC, *et al*. 2005 Epigenetic differences arise during the lifetime of monozygotic twins. *PNAS* **102** 10604–10609

Frank SA 2010 Somatic evolutionary genomics: mutations during development cause highly variable genetic mosaicism with risk of cancer and neurodegeneration. *PNAS* **107** 1725–1730

Fraser D and Kærn M 2009 A chance at survival: gene expression noise and phenotypic diversification strategies. *Mol. Microbiol.* **71** 1333–1340

Fraser HB, Hirsh AE, Giaever G, Kumm J and Eisen MB 2004 Noise minimization in eukaryotic gene expression. *PLoS Biol.* **2** 834–838

Freed NE, Silander OK, Stecher B, Böhm A, Hardt W-D and Ackermann M 2008 A simple screen to identify promoters conferring high levels of phenotypic noise. *PLoS Genet.* **4** e1000307

Freeman DC, Graham JH and Emlen JM 1993 Developmental stability in plants: symmetries, stress and epigenesis. *Genetica* **89** 97–119

Fridley JD, Stachowicz JJ, Naeem S, Sax DF, Seabloom EW, Smith MD, Stohlgren TJ, Tilman D, *et al*. 2007 The invasion paradox: reconciling pattern and process in species invasions. *Ecology* **88** 3–17

Fungairiño SG, Fernández C, Serrano JM, López F and Acosta FJ 2005 Developmental instability and plant potential fitness in a Mediterranean perennial plant, *Retama sphaerocarpa* (L.) Boiss. *Acta Oecol.* **27** 43–48

Fusco G and Minelli A 2010 Phenotypic plasticity in development and evolution: facts and concepts. *Phil. Trans. R. Soc. B* **365** 547–556

Galton F 1876 The history of twins, as a criterion of the relative powers of nature and nurture. *J. Anthropol. Inst. GB Ireland* **5** 391–406

Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, Farinelli L, Miska E, *et al*. 2014 Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. *Nat. Neurosci.* **17** 667–669

Gärtner K 1985 Versuchstierkunde und 'intangible variance'– eine dritte Komponente der kontinuierlichen Variabilität neben Erbgut und Umwelt. *Verh. Dtsch. Zool. Ges.* **78** 61–75

Gärtner K 1990 A third component causing random variability beside environment and genotype. A reason for the limited success of a 30 year long effort to standardize laboratory animals? *Lab. Anim.* **24** 71–77

Gärtner K 2012 Commentary: Random variability of quantitative characteristics, an intangible epigenomic product, supporting adaptation. *Int. J. Epidemiol.* **41** 342–346

Gärtner K, Bube P, Flamme A, Peters K and Pfaff J 1976 Komponenten biologischer Variabilität und die Grenzen ihrer Manipulierbarkeit. *Z. Versuchstierk.* **18** 146–158

Gärtner K, Ostheimer C and Rapp K 1991 Der Einfluß der uterinen Umwelt auf Körperlängen und Körpergewicht, untersucht an monozygoten Rinderzwillingen nach Embryotransfer auf eine oder zwei Ammen. *Reprod. Domest. Anim.* **26** 235–250

Ghalambor CK, McKay JK, Carroll SP and Reznick DN 2007 Adaptive versus non-adaptive phenotypic plasticity and the potential for contemporary adaptation in new environments. *Funct. Ecol.* **21** 394–407

Gierer A and Meinhardt H 1972 A theory of biological pattern formation. *Kybernetik* **12** 30–39

Gilbert JJ and Schröder T 2007 Intraclonal variation in propensity for mixis in several rotifers: variation among females and with maternal age. *Hydrobiol.* **593** 121–128

Gill DE, Chao L, Perkins SL and Wolf JB 1995 Genetic mosaicism in plants and clonal animals. *Annu. Rev. Ecol. Syst.* **26** 423–444

Goll MG and Bestor TH 2005 Eukaryotic cytosine methyltransferases. *Annu. Rev. Biochem.* **74** 481–514

Görür G 2009 Zinc and cadmium accumulation in cabbage aphid (*Brevicoryne brassicae*) host plants and developmental instability. *Insect Sci.* **16** 65–71

Gosling SD 2008 Personality in non-human animals. *Soc. Pers. Psychol. Compass* **2** 985–1001

Gould SJ and Lloyd EA 1999 Individuality and adaptation across levels of selection: how shall we name and generalize the unit of Darwinism? *PNAS* **96** 11904–11909

Graham JH, Raz S, Hel-Or H and Nevo E 2010 Fluctuating asymmetry: methods, theory, and applications. *Symmetry* **2** 466–540

Grüneberg H 1954 Variation within inbred strains of mice. *Nature* **173** 674–676

Hageman SJ, Bayer MM and Todd CD 1999 Partitioning phenotypic variation: genotypic, environmental and residual components from bryozoan skeletal morphology. *J. Nat. Hist.* **33** 1713–1735

Haig D 2007 Weismann rules! Ok? Epigenetics and the Lamarckian temptation. *Biol. Phil.* **22** 415–428

Hall MC, Dworkin I, Ungerer MC and Purugganan M 2007 Genetics of microenvironmental canalization in *Arabidopsis thaliana*. *PNAS* **104** 13717–13722

Hallgrímsson B and Hall BK (eds) 2005 *Variation: a central concept in biology* (New York: Elsevier Academic Press)

Hallgrímsson B and Hall BK (eds) 2011a *Epigenetics: linking genotype and phenotype in development and evolution* (Berkeley: University of California Press)

Hallgrímsson B and Hall BK 2011b Epigenetics: the context of development; in *Epigenetics: linking genotype and phenotype in development and evolution* (eds) B Hallgrímsson and BK Hall (Berkely: University of California Press) pp 424–438

Hammel JU, Herzen J, Beckmann F and Nickel M 2009 Sponge budding is a spatiotemporal morphological patterning process: insights from synchrotron radiation-based x-ray microtomography into the asexual reproduction of *Tethya wilhelma*. *Front. Zool.* **6** 19

Hansen KD, Timp W, Corrada Bravo H, Sabunciyan S, Langmead B, McDonald OG, Wen B, Wu H, *et al*. 2011 Increased methylation variation in epigenetic domains across cancer types. *Nat. Genet.* **43** 768–775

Hauser M-T, Aufsatz W, Jonak C and Luschnig C 2011 Transgenerational epigenetic inheritance in plants. *Biochim. Biophys. Acta* **1809** 459–468

Heithoff DM, Sinsheimer RL, Low DA and Mahan MJ 1999 An essential role for DNA adenine methylation in bacterial virulence. *Science* **284** 967–970

Henderson IR and Jacobsen SE 2007 Epigenetic inheritance in plants. *Nature* **447** 418–424

Hendrikse JL, Parsons TE and Hallgrímsson B 2007 Evolvability as the proper focus of evolutionary developmental biology. *Evol. Dev.* **9** 393–401

Herman JJ, Spencer HG, Donohue K and Sultan SE 2014 How stable 'should' epigenetic modifications be? Insights from adaptive plasticity and bet hedging. *Evolution* **68** 632–643

Hernández-Hernández V, Niklas KJ, Newman SA and Benítez M 2012 Dynamical patterning modules in plant development and evolution. *Int. J. Dev. Biol.* **56** 661–674

Herndon LA, Schmeissner PJ, Dudaronek JM, Brown PA, Listner KM, Sakano Y, Paupard MC, Hall DH, *et al*. 2002 Stochastic and genetic factors influence tissue-specific decline in ageing *C. elegans*. *Nature* **419** 808–814

Herranz H and Cohen SM 2010 MicroRNAs and gene regulatory networks: managing the impact of noise in biological systems. *Genes Dev.* **24** 1339–1344

Hiendleder S 2007 Mitochondrial DNA inheritance after SCNT. *Adv. Exp. Med. Biol.* **591** 103–116

Hirsch S, Baumberger R and Grossniklaus U 2012 Epigenetic variation, inheritance, and selection in plant populations. *Cold Spring Harb. Symp. Quant. Biol.* **77** 97–104

Ho AS, Turcan S and Chan TA 2013 Epigenetic therapy: use of agents targeting deacetylation and methylation in cancer management. *OncoTargets Ther.* **6** 223–232

Hoffmann AA, Reynolds KT, Nash MA and Weeks AR 2008 A high incidence of parthenogenesis in agricultural pests. *Proc. R. Soc. B* **275** 2473–2481

Hornstein E and Shomron N 2006 Canalization of development by microRNAs. *Nat. Genet.* **38** S20–24

Huang S 2009 Non-genetic heterogeneity of cells in development: more than just noise. *Development* **136** 3853–3862

Hughes RN 1989 *A functional biology of clonal animals* (London: Chapman and Hall)

Huh D and Paulsson J 2011 Non-genetic heterogeneity from stochastic partitioning at cell division. *Nat. Genet.* **43** 95–100

Hull DL 1980 Individuality and selection. *Annu. Rev. Ecol. Syst.* **11** 311–332

Hunt BG, Brisson JA, Yi SV and Goodisman MAD 2010 Functional conservation of DNA methylation in the pea aphid and the honeybee. *Genome Biol. Evol.* **2** 719–728

Iguchi K, Matsubara N and Hakoyama H 2001 Behavioural individuality assessed from two strains of cloned fish. *Anim. Behav.* **61** 351–356

Indrasamy H, Woods RE, McKenzie JA and Batterham P 2000 Fluctuating asymmetry for specific bristle characters in *Notch* mutants of *Drosophila melanogaster. Genetica* **109** 151–159

Jablonka E 2012 Epigenetic variations in heredity and evolution. *Clin. Pharmacol. Therapeut.* **92** 683–688

Jablonka E and Lamb MJ 2014 *Evolution in four dimensions: genetic, epigenetic, behavioral, and symbolic variation in the history of life, revised edition* (Cambridge: MIT Press)

Jablonka E and Raz G 2009 Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. *Quart. Rev. Biol.* **84** 131–176

Jaenisch R and Bird A 2003 Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat. Genet.* **33** 245–254

Jain AK, Prabhakar S and Pankanti S 2002 On the similarity of identical twin fingerprints. *Pattern Recog.* **35** 2653–2663

Johannsen W 1913 *Elemente der exakten Erblichkeitslehre, mit Grundzügen der biologischen Variationsstatistik*, 2. Ausgabe (Jena: Gustav Fischer Verlag)

Johnston RJ Jr and Desplan C 2010 Stochastic mechanisms of cell fate specification that yield random or robust outcomes. *Annu. Rev. Cell Dev. Biol.* **26** 689–719

Johnston IG, Gaal B, das Neves RP, Enver T, Iborra FJ and Jones NS 2012 Mitochondrial variability as a source of extrinsic cellular noise. *PLoS Comput. Biol.* **8** e1002416

Jones JPG, Rasamy JR, Harvey A, Toon A, Oidtmann B, Randrianarison MH, Raminosoa N and Ravoahangimalala OR 2009 The perfect invader: a parthenogenic crayfish poses a new threat to Madagascar's freshwater biodiversity. *Biol. Invasions* **11** 1475–1482

Kaelin CB and Barsh GS 2013 Genetics of pigmentation in dogs and cats. *Annu. Rev. Anim. Biosci.* **1** 125–156

Kærn M, Elston TC, Blake WJ and Collins JJ 2005 Stochasticity in gene expression: from theories to phenotypes. *Nat. Rev. Genet.* **6** 451–464

Kaminsky ZA, Tang T, Wang S-C, Ptak C, Oh GHT, Wong AHC, Feldcamp LA, Virtanen C, *et al*. 2009 DNA methylation profiles in monozygotic and dizygotic twins. *Nat. Genet.* **41** 240–245

Kaneko K and Furusawa C 2008 Relevance of phenotypic noise to adaptation and evolution. *IET Syst. Biol.* **2** 234–246

Karp A 1994 Origins, causes and uses of variation in plant tissue cultures; in *Plant cell and tissue culture* (eds) IK Vasil and AT Thorpe (Dordrecht: Springer) pp 139–151

Kasbekar DP, Madigan S and Katz ER 1985 Self-induced nystatin resistance in *Dictyostelium discoideum*. *Antimicrob. Agents Chemother*. **27** 974–976

Kenrick P and Crane PR 1997 The origin and early evolution of plants on land. *Nature* **389** 33–39

Kilfoil ML, Lasko P and Abouheif E 2009 Stochastic variation: from single cells to superorganisms. *HFSP J.* **3** 379–385

Kim KH and Sauro HM 2012 Adjusting phenotypes by noise control. *PLoS Comput. Biol.* **8** e1002344

Kirkwood TBL 2012 Commentary: Ageing – what's all the noise about? Developments after Gärtner. *Int. J. Epidemiol.* **41** 351–352

Kirkwood TBL and Finch CE 2002 The old worm turns more slowly. *Nature* **419** 794–795

Kirkwood TBL, Feder M, Finch CE, Franceschi C, Globerson A, Klingenberg CP, LaMarco K, Omholt S, *et al*. 2005 What accounts for the wide variation in life span of genetically identical organisms reared in a constant environment? *Mech. Ageing Dev.* **126** 439–443

Kitano H 2004 Biological robustness. *Nat. Rev. Genet.* **5** 826–837

Klingenberg CP 2003 A developmental perspective on developmental instability: theory, models and mechanisms; in *Developmental instability: causes and consequences* (ed) M Polak (Oxford: Oxford University Press) pp 14–34

Klingenberg CP 2006 Dominance, nonlinear developmental mapping and developmental stability; in *The biology of genetic dominance* (ed) RA Veitia (Georgetown: Landes Bioscience) pp 37–51

Knoll AH, Javaux EJ, Hewitt D and Cohen P 2006 Eukaryotic organisms in Proterozoic oceans. *Phil. Trans. R. Soc. B* **361** 1023–1038

Koehler AV, Springer YP, Keeney DB and Poulin R 2011 Intra- and interclonal phenotypic and genetic variability of the trematode *Maritrema novaezealandensis. Biol. J. Linn. Soc.* **103** 106–116

Kohli RM and Zhang Y 2013 TET enzymes, TDG and the dynamics of DNA demethylation. *Nature* **502** 472–479

Kong AW-K, Zhang D and Lu G 2006 A study of identical twins' palmprints for personal verification. *Pattern Recog.* **39** 2149–2156

Koonin EV 2012 *The logic of chance: the nature and origin of biological evolution* (Upper Saddle River: Pearson Education)

Koonin EV, Senkevich TG and Dolja VV 2006 The ancient Virus World and evolution of cells. *Biol. Direct* **1** 29

Kovalchuk I 2012 Transgenerational epigenetic inheritance in animals. *Front. Genet.* **3** 76

Kroes R, Galli C, Munro I, Schilter B, Tran L-A, Walker R and Würtzen G 2000 Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. *Food Chem. Toxicol.* **38** 255–312

Kücken M 2007 Models for fingerprint pattern formation. *Forensic Sci. Int.* **171** 85–96

Kupiec J-J 2009 *The origin of individuals* (Singapore: World Scientific)

Laird PW 2010 Principles and challenges of genome-wide DNA methylation analysis. *Nat. Rev. Genet.* **11** 191–203

Lajus DL and Alekseev VR 2004 Phenotypic variation and developmental instability of life-history traits: a theory and a case study on within-population variation of resting eggs formation in *Daphnia. J. Limnol.* **63** 37–44

Lande R, Engen S and Sæther B-E 2003 *Stochastic population dynamics in ecology and conservation* (Oxford: Oxford University Press)

Landry CR and Rifkin SA 2012 The genotype-phenotype maps of systems biology and quantitative genetics: distinct and complementary. *Adv. Exp. Med. Biol.* **751** 371–398

Landry AM, Landry DJ, Gentry LR, Green HL, Reggio B, Koonce KL, Echelard Y and Godke RA 2005 Endocrine profiles and growth patterns of cloned goats. *Clon. Stem Cells* **7** 214–225

Larkin PJ and Scowcroft WR 1981 Somaclonal variation – a novel source of variability from cell cultures for plant improvement. *Theor. Appl. Genet.* **60** 197–214

Larsen E 2005 Developmental origins of variation; in *Variation: a central concept in biology* (eds) B Hallgrímsson and BK Hall (New York: Elsevier Academic Press) pp 113–129

Latzel V, Allan E, Silveira AB, Colot V, Fischer M and Bossdorf O 2013 Epigenetic diversity increases the productivity and stability of plant populations. *Nat. Commun.* **4** 2875

Lawrence JG and Retchless AC 2009 The interplay of homologous recombination and horizontal gene transfer in bacterial speciation. *Meth. Mol. Biol.* **532** 29–53

Leamy LJ and Klingenberg CP 2005 The genetics and evolution of fluctuating asymmetry. *Annu. Rev. Ecol. Evol. Syst.* **36** 1–21

Leamy LJ, Meagher S, Taylor S, Carroll L and Potts WK 2001 Size and fluctuating asymmetry of morphometric characters in mice: their associations with inbreeding and *t*-haplotype. *Evolution* **55** 2333–2341

LeDoux J 2002 *Synaptic self: how our brains become who we are* (New York: Penguin)

Lee H, Popodi E, Tang H and Foster PL 2012 Rate and molecular spectrum of spontaneous mutations in the bacterium *Escherichia coli* as determined by whole-genome sequencing. *PNAS* **109** E2774–2783

Lehner B 2010 Conflict between noise and plasticity in yeast. *PLoS Genet.* **6** e1001185

Lennartsson A and Ekwall K 2009 Histone modification patterns and epigenetic codes. *Biochim. Biophys. Acta* **1790** 863–868

Lenormand T, Roze D and Rousset F 2009 Stochasticity in evolution. *Trends Ecol. Evol.* **24** 157–165

Levy SF and Siegal ML 2008 Network hubs buffer environmental variation in *Saccharomyces cerevisiae. PLoS Biol.* **6** e264

Lewejohann L, Zipser B and Sachser N 2011 "Personality" in laboratory mice used for biomedical research: a way of understanding variability? *Dev. Psychobiol.* **53** 624–630

Lewontin RC 1970 The units of selection. *Annu. Rev. Ecol. Syst.* **1** 1–18

Lewontin RC 2000 *The triple helix: gene, organism, and environment* (Cambridge: Harvard University Press)

Lewus P and Ford RM 1999 Temperature-sensitive motility of *Sulfolobus acidocaldarius* influences population distribution in extreme environments. *J. Bacteriol.* **181** 4020–4025

Li X, Cassidy JJ, Reinke CA, Fischboeck S and Carthew RW 2009 A microRNA imparts robustness against environmental fluctuation during development. *Cell* **137** 273–282

Li J, Min R, Vizeacoumar FJ, Jin K, Xin X and Zhang Z 2010 Exploiting the determinants of stochastic gene expression in *Saccharomyces cerevisiae* for genome-wide prediction of expression noise. *PNAS* **107** 10472–10477

Libby E and Rainey PB 2011 Exclusion rules, bottlenecks and the evolution of stochastic phenotype switching. *Proc. R. Soc. B* **278** 3574–3583

Liebl AL, Schrey AW, Richards CL and Martin LB 2013 Patterns of DNA methylation throughout a range expansion of an introduced songbird. *Integr. Comp. Biol.* **53** 351–358

Lim JP and Brunet A 2013 Bridging the transgenerational gap with epigenetic memory. *Trends Genet.* **29** 176–186

López-Garrido J, Cota I and Casadesús J 2012 Epigenetic gene regulation in bacteria; in *Epigenetic regulation and epigenomics* (ed) RA Meyers (Weinheim: Wiley-VHC) pp 1107–1138

Losick R and Desplan C 2008 Stochasticity and cell fate. *Science* **320** 65–68

Lyko F, Foret S, Kucharski R, Wolf S, Falckenhayn C and Maleszka R 2010 The honey bee epigenomes: differential methylation of brain DNA in queens and workers. *PLoS Biol.* **8** e1000506

Lynch M and Conery JS 2000 The evolutionary fate and consequences of duplicate genes. *Science* **290** 1151–1155

Lynch M, Sung W, Morris K, Coffey N, Landry CR, Dopman EB, Dickinson WJ, Okamoto K, *et al*. 2008 A genome-wide view of the spectrum of spontaneous mutations in yeast. *PNAS* **105** 9272–9277

Maamar H, Raj A and Dubnau D 2007 Noise in gene expression determines cell fate in *Bacillus subtilis. Science* **317** 526–529

Macagno ER, Lopresti V and Levinthal C 1973 Structure and development of neuronal connections in isogenic organisms: variations and similarities in the optic system of *Daphnia magna. Proc. Natl. Acad. Sci. USA* **70** 57–61

Mahner M and Kary M 1997 What exactly are genomes, genotypes and phenotypes? And what about phenomes? *J. Theor. Biol.* **186** 55–63

Maiti S, Kumar KHBG, Castellani CA, O'Reilly R and Singh SM 2011 Ontogenetic *de novo* copy number variations (CNVs) as a source of genetic individuality: studies on two families with MZD twins for schizophrenia. *PLoS ONE* **6** e17125

Malandrin L, Huber H and Bernander R 1999 Nucleoid structure and partition in *Methanococcus jannaschii*: an archaeon with multiple copies of the chromosome. *Genetics* **152** 1315–1323

Margulis L and Schwartz KV 1997 *Five kingdoms: an illustrated guide to the phyla of life on earth*, 3rd ed. (San Francisco: WH Freeman)

Markow TA and Gottesman II 1989 Dermatoglyphic fluctuating asymmetry in twins and singletons. *Hereditas* **110** 211–215

Mark Welch DB and Meselson M 2000 Evidence for the evolution of bdelloid rotifers without sexual reproduction or genetic exchange. *Science* **288** 1211–1215

Marshall WL and Berbee ML 2010 Population-level analyses indirectly reveal cryptic sex and life history traits of *Pseudoperkinsus tapetis* (Ichthyosporea, Opisthokonta): a unicellular relative of the animals. *Mol. Biol. Evol.* **27** 2014–2026

Martin GM 2009 Epigenetic gambling and epigenetic drift as an antagonistic pleiotropic mechanism of aging. *Aging Cell* **8** 761–764

Martin GM 2014 Nature, nurture, and chance: their roles in interspecific and intraspecific modulations of aging. *Ann. Rev. Gerontol. Geriat.* **34** 267–284

Marusyk A, Almendro V and Polyak K 2012 Intra-tumour heterogeneity: a looking glass for cancer? *Nat. Rev. Cancer* **12** 323–334

Maves L and Schubiger G 1998 A molecular basis for transdetermination in *Drosophila* imaginal discs: interactions between *wingless* and *decapentaplegi*c signaling. *Development* **125** 115–124

Maynard Smith J, Smith NH, O'Rourke M and Spratt BR 1993 How clonal are bacteria? *Proc. Natl. Acad. Sci. USA* **90** 4384–4388

McAdams HH and Arkin A 1997 Stochastic mechanisms in gene expression. *Proc. Natl. Acad. Sci. USA* **94** 814–819

McCrae RR, Jang KL, Livesley WJ, Riemann R and Angleitner A 2001 Sources of structure: genetic, environmental, and artifactual influences on the covariation of personality traits. *J. Pers.* **69** 511–535

Medrano M, Herrera CM and Bazaga P 2014 Epigenetic variation predicts regional and local intraspecific functional diversity in a perennial herb. *Mol. Ecol.* **23** 4926–4938

Meinhardt H 2009 *The algorithmic beauty of sea shells,* 4th ed. (Berlin: Springer)

Meng TC, Somani S and Dhar P 2004 Modeling and simulation of biological systems with stochasticity. *In Silico Biol.* **4** 24

Mergeay J, Verschuren D and De Meester L 2006 Invasion of an asexual American water flea clone throughout Africa and rapid displacement of a native sibling species. *Proc. R. Soc. B* **273** 2839–2844

Meyer HM and Roeder AHK 2014 Stochasticity in plant cellular growth and patterning. *Front. Plant Sci.* **5** 420

Miguel C and Marum L 2011 An epigenetic view of plant cells cultured in vitro: somaclonal variation and beyond. *J. Exp. Bot.* **62** 3713–3725

Milán M, Campuzano S and García-Bellido A 1996 Cell cycling and patterned cell proliferation in the wing primordium of *Drosophila. Proc. Natl. Acad. Sci. USA* **93** 640–645

Miller-Jensen K, Dey SS, Schaffer DV and Arkin AP 2011 Varying virulence: epigenetic control of expression noise and disease processes. *Trends Biotechnol.* **29** 517–525

Miller-Jensen K, Skupsky R, Shah PS, Arkin AP and Schaffer DV 2013 Genetic selection for context-dependent stochastic phenotypes: Sp1 and TATA mutations increase phenotypic noise in HIV-1 gene expression. *PLoS Comput. Biol.* **9** e1003135

Mills SK and Beatty JH 1979 The propensity interpretation of fitness. *Phil. Sci.* **46** 263–286

Milton CC, Huynh B, Batterham P, Rutherford SL and Hoffmann AA 2003 Quantitative trait symmetry independent of Hsp90 buffering: distinct modes of genetic canalization and developmental stability. *PNAS* **100** 13396–13401

Milton CC, Ulane CM and Rutherford S 2006 Control of canalization and evolvability by Hsp90. *PLoS ONE* **1** e75

Molenaar PCM, Boomsma DI and Dolan CV 1993 A third source of developmental differences. *Behav. Genet.* **23** 519–524

Moore RC and Purugganan MD 2005 The evolutionary dynamics of plant duplicate genes. *Curr. Opin. Plant Biol.* **8** 122–128

Müller GB and Newman SA 2003 *Origination of organismal form: beyond the gene in development and evolutionary biology* (Cambridge: MIT Press)

Murray JD 2003 *Mathematical biology. II: Spatial models and biomedical applications,* 3rd ed. (New York: Springer)

Nanjundiah V 2003 Phenotypic plasticity and evolution by genetic assimilation; in *Origination of organismal form: beyond the gene in development and evolutionary biology* (eds) GB Müller and SA Newman (Cambridge: MIT Press) pp 245–264

Nanjundiah V and Bhogle AS 1995 The precision of regulation in *Dictyostelium discoideum*: implications for cell-type proportioning in the absence of spatial pattern. *Ind. J. Biochem. Biophys.* **32** 404–416

Nanjundiah V and Newman SA 2009 Forword *Special Issue on Phenotypic and Developmental Plasticity. J. Biosci.* **34** 493–494

Neildez-Nguyen TMA, Parisot A, Vignal C, Rameau P, Stockholm D, Picot J, Allo V, Le Bec C, *et al*. 2008 Epigenetic gene expression noise and phenotypic diversification of clonal cell populations. *Differentiation* **76** 33–40

Newman HH 1913 The modes of inheritance of aggregates of meristic (integral) variates in the polyembryonic offspring of the nine-banded armadillo. *J. Exp. Zool.* **15** 145–192

Newman SA and Bhat R 2007 Activator-inhibitor dynamics of vertebrate limb pattern formation. *Birth Defects Res. C* **81** 305–319

Newman SA and Müller GB 2000 Epigenetic mechanisms of character origination. *J. Exp. Zool. B (Mol. Dev. Evol.)* **288** 304–317

Newman SA and Müller GB 2005 Origination and innovation in the vertebrate limb skeleton: an epigenetic perspective. *J. Exp. Zool. B (Mol. Dev. Evol.)* **304** 593–609

Newman HH and Patterson JT 1909 A case of normal identical quadruplets in the nine-banded armadillo, and its bearing on the problems of identical twins and of sex determination. *Biol. Bull.* **17** 181–187

Newman JRS, Ghaemmaghami S, Ihmels J, Breslow DK, Noble M, DeRisi JL and Weissman JS 2006 Single-cell proteomic analysis of *S. cerevisiae* reveals the architecture of biological noise. *Nature* **441** 840–846

Niepel M, Spencer SL and Sorger PK 2009 Non-genetic cell-to-cell variability and the consequences for pharmacology. *Curr. Opin. Chem. Biol.* **13** 556–561

Nijhout HF, Maini PK, Madzvamuse A, Wathen AJ and Sekimura T 2003 Pigmentation pattern formation in butterflies: experiments and models. *C. R. Biol.* **326** 717–727

Nikel PI, Silva-Rocha R, Benedetti I and de Lorenzo V 2014 The private life of environmental bacteria: pollutant biodegradation at the single cell level. *Environ. Microbiol.* **16** 628–642

Ning L, Liu G, Li G, Hou Y, Tong Y and He J 2014 Current challenges in the bioinformatics of single cell genomics. *Front. Oncol.* **4** 7

Novick A and Weiner M 1957 Enzyme induction as an all-or-none phenomenon. *Proc. Natl. Acad. Sci. USA* **43** 553–566

O'Connor TD and Mundy NI 2009 Genotype-phenotype associations: substitution models to detect evolutionary associations between phenotypic variables and genotypic evolutionary rate. *Bioinformatics* **25** i94–100

Oey H and Whitelaw E 2012 Commentary: Gärtner's 'third component': still an open question. *Int. J. Epidemiol.* **41** 356–358

Orias E and Bradshaw AD 1992 Stochastic developmental variation in the ratio of allelic rDNAs among newly differentiated, heterozygous macronuclei of *Tetrahymena thermophila. Dev. Genet.* **13** 87–93

Osella M, Bosia C, Corá D and Caselle M 2011 The role of incoherent microRNA-mediated feedforward loops in noise buffering. *PLoS Comput. Biol.* **7** e1001101

Overton WF 1973 On the assumptive base of the nature-nurture controversy: additive versus interactive conceptions. *Hum. Dev.* **16** 74–89

Paigen K 2003 One hundred years of mouse genetics: an intellectual history. I. The classical period (1902-1980). *Genetics* **163** 1–7

Palmer AR and Strobeck C 1986 Fluctuating asymmetry: measurement, analysis, patterns. *Ann. Rev. Ecol. Syst.* **17** 391–421

Parsons PA 1992 Fluctuating asymmetry: a biological monitor of environmental and genomic stress. *Heredity* **68** 361–364

Patnaik PR 2006 External, extrinsic and intrinsic noise in cellular systems: analogies and implications for protein synthesis. *Biotechnol. Mol. Biol. Rev.* **1** 121–127

Patra P and Klumpp S 2013 Population dynamics of bacterial persistence. *PLoS ONE* **8** e62814

Patterson JS and Klingenberg CP 2007 Developmental buffering: how many genes? *Evol. Dev.* **9** 525–526

Pearl R 1906 Variation in *Chilomonas* under favourable and unfavourable conditions. *Biometrika* **5** 53–72

Pearson K, Lee A, Warren E, Fry A and Fawcett CD 1901 Mathematical contributions to the theory of evolution. IX. On the principle of homotyposis and its relation to heredity, to the variability of the individual, and to that of the race. Part I. Homotyposis in the vegetable kingdom. *Proc. R. Soc.* **68** 1–5

Peaston AE and Whitelaw E 2006 Epigenetics and phenotypic variation in mammals. *Mamm. Genome* **17** 365–374

Pfennig DW and Servedio MR 2013 The role of transgenerational epigenetic inheritance in diversification and speciation. *Non-Genet. Inherit.* **1** 17–26

Piersma T and van Gils JA 2011 *The flexible phenotype: a body centred integration of ecology, physiology, and behaviour* (Oxford: Oxford University Press)

Pietrzak B 2011 Interclonal differences in age-specific performance in *Daphnia magna*. *J. Limnol. Spec. Insert* **70** 345–352

Pigliucci M 2001 *Phenotypic plasticity: beyond nature and nurture* (Baltimore: Johns Hopkins University Press)

Pigliucci M 2010 Genotype-phenotype mapping and the end of the 'genes as blueprint' metaphor. *Phil. Trans. R. Soc. B.* **365** 557–566

Pigliucci M and Müller GB (eds) 2010 *Evolution: the extended synthesis* (Cambridge: MIT Press)

Pigliucci M, Murren CJ and Schlichting CD 2006 Phenotypic plasticity and evolution by genetic assimilation. *J. Exp. Biol.* **209** 2362–2367

Pilbrough W, Munro TP and Gray P 2009 Intraclonal protein expression heterogeneity in recombinant CHO cells. *PLoS ONE* **4** e8432

Pimentel D 2005 Environmental and economic costs of the application of pesticides primarily in the United States. *Environ. Dev. Sustain.* **7** 229–252

Pimentel D, McNair S, Janecka J, Wightman J, Simmonds C, O'Connell C, Wong E, Russel L, *et al*. 2001 Economic and environmental threats of alien plant, animal, and microbe invasions. *Agric. Ecosyst. Environ.* **84** 1–20

Plomin R 2011 Commentary: Why are children in the same family so different? Non-shared environment three decades later. *Int. J. Epidemiol.* **40** 582–592

Plomin R and Daniels D 1987 Why are children in the same family so different from one another? *Behav. Brain Sci.* **10** 1–60

Ponczek LM and Blackstone NW 2001 Effect of cloning rate on fitness-related traits in two marine hydroids. *Biol. Bull.* **201** 76–83

Probst AV, Dunleavy E and Almouzni G 2009 Epigenetic inheritance during the cell cycle. *Nat. Rev. Mol. Cell Biol.* **10** 192–206

Pujadas E and Feinberg AP 2012 Regulated noise in the epigenetic landscape of development and disease. *Cell* **148** 1123–1131

Queitsch C, Sangster TA and Lindquist S 2002 Hsp90 as a capacitor of phenotypic variation. *Nature* **417** 618–624

Raddatz G, Guzzardo PM, Olova N, Fantappié MR, Rampp M, Schaefer M, Reik W, Hannon GJ, *et al*. 2013 Dnmt2-dependent methylomes lack defined DNA methylation patterns. *PNAS* **110** 8627–8631

Ràfols I, MacWilliams HK, Maeda Y and Sawada Y 2014 On the conflict between precision and robustness in the proportion regulation of cell types. *arXiv* 1401.7872

Raj A and van Oudenaarden A 2008 Nature, nurture, or chance: stochastic gene expression and its consequences. *Cell* **135** 216–226

Rakyan VK, Blewitt ME, Druker R, Preis JI and Whitelaw E 2002 Metastable epialleles in mammals. *Trends Genet.* **18** 348–351

Raser JM and O'Shea EK 2005 Noise in gene expression: origins, consequences, and control. *Science* **309** 2010–2013

Reed DR, Bachmanov AA and Tordoff MG 2007 Forty mouse strain survey of body composition. *Physiol. Behav.* **91** 593–600

Reeve ECR and Robertson FW 1954 Studies in quantitative inheritance VI. Sternite chaeta number in *Drosophila*: a metameric quantitative character. *Z. indukt. Abst. Vererbungsl.* **86** 269–288

Richard M and Yvert G 2014 How does evolution tune biological noise? *Front. Genet.* **5** 374

Riis T, Lambertini C, Olesen B, Clayton JS, Brix H and Sorrell BK 2010 Invasion strategies in clonal aquatic plants: are phenotypic differences caused by phenotypic plasticity or local adaptation? *Ann. Bot.* **106** 813–822

Ringrose L and Paro R 2007 Polycomb/Trithorax response elements and epigenetic memory of cell identity. *Development* **134** 223–232

Ripa J, Olofsson H and Jonzén N 2010 What is bet-hedging, really? *Proc. R. Soc. B* **277** 1153–1154

Rodin SN and Riggs AD 2003 Epigenetic silencing may aid evolution by gene duplication. *J. Mol. Evol.* **56** 718–729

Rodríguez López CM, Wetten AC and Wilkinson MJ 2010 Progressive erosion of genetic and epigenetic variation in callus-derived cocoa (*Theobroma cacao*) plants. *New Phytol.* **186** 856–868

Rollo CD 1995 *Phenotypes: their epigenetics, ecology and evolution* (New York: Chapman and Hall)

Roth C, Rastogi S, Arvestad L, Dittmar K, Light S, Ekman D and Liberles DA 2007 Evolution after gene duplication: models, mechanisms, sequences, systems, and organisms. *J. Exp. Zool. B. (Mol. Dev. Evol.)* **308** 58–73

Roy SK 1963 The variation of organs of individual plants. *J. Genet.* **58** 147–176

Rubin H 1990 The significance of biological heterogeneity. *Cancer Metastasis Rev.* **9** 1–20

Rubin GM and Lewis EB 2000 A brief history of *Drosophila's* contributions to genome research. *Science* **287** 2216–2218

Sablowski R 2004 Plant and animal stem cells: conceptually similar, molecularly distinct? *Trends Cell Biol.* **14** 605–611

Sahijram L, Soneji JR and Bollamma KT 2003 Analyzing somaclonal variation in micropropagated bananas (*Musa* spp.). *In Vitro Cell Dev. Biol. Plant* **39** 551–556

Sakai K-I and Shimamoto Y 1965 Developmental instability in leaves and flowers of *Nicotiana tabacum. Genetics* **51** 801–813

Sakai AK, Allendorf FW, Holt JS, Lodge DM, Molofsky J, With KA, Baughman S, Cabin RJ, *et al*. 2001 The population biology of invasive species. *Annu. Rev. Ecol. Syst.* **32** 305–332

Salathia N and Queitsch C 2007 Molecular mechanisms of canalization: Hsp90 and beyond. *J. Biosci.* **32** 457–463

Sangster TA, Salathia N, Undurraga S, Milo R, Schellenberg K, Lindquist S and Queitsch C 2008 HSP90 affects the expression of genetic variation and developmental stability in quantitative traits. *PNAS* **105** 2963–2968

Saunders E, Tindall BJ, Fähnrich R, Lapidus A, Copeland A, *et al.* 2010 Complete genome sequence of *Haloterrigena turkmenica* type strain ($4k^T$). *Stand. Genomic Sci.* **2** 107–116

Saze H 2008 Epigenetic memory transmission through mitosis and meiosis in plants. *Sem. Cell Dev. Biol.* **19** 527–536

Scheiner SM 1993 Genetics and evolution of phenotypic plasticity. *Annu. Rev. Ecol. Syst.* **24** 35–68

Schilthuizen M and Gravendeel B 2012 Left-right asymmetry in plants and animals: a gold mine for research. *Contrib. Zool.* **81** 75–78

Schimz A and Hildebrand E 1992 Nonrandom structures in the locomotor behavior of *Halobacterium*: a bifurcation route to chaos? *Proc. Natl. Acad. Sci. USA* **89** 457–460

Schlichting CD and Pigliucci M 1998 *Phenotypic evolution: a reaction norm perspective* (Sunderland: Sinauer Associates)

Schlichting CD and Wund MA 2014 Phenotypic plasticity and epigenetic marking: an assessment of evidence for genetic accomodation. *Evolution* **68** 656–672

Scholtz G 1992 Cell lineage studies in the crayfish *Cherax destructor* (Crustacea, Decapoda): germ band formation, segmentation, and early neurogenesis. *Roux's Arch. Dev. Biol.* **202** 36–48

Schön I, Martens K and van Dijk P (eds) 2009 *Lost sex: the evolutionary biology of parthenogenesis* (Dordrecht: Springer)

Schuett W, Dall SRX, Baeumer J, Kloesener MH, Nakagawa S, Beinlich F and Eggers T 2011 'Personality' variation in a clonal insect: the pea aphid, *Acyrthosiphon pisum. Dev. Psychobiol.* **53** 631–640

Seidel GE Jr 2002 Genetic and phenotypic similarity among members of mammalian clonal sets; in *Principles of cloning* (eds) J Cibelli, RP Lanza, KHS Campbell and MD West (Amsterdam: Academic Press) pp 215–225

Seidel GE Jr, Elsden RP and Hasler JF 2003 *Embryo transfer in dairy cattle* (Fort Atkinson: Hoards and Sons)

Sharma A 2013 Transgenerational epigenetic inheritance: focus on soma to germline information transfer. *Progr. Biophys. Mol. Biol.* **113** 439–446

Shelton DE, Desnitskiy AG and Michod RE 2012 Distributions of reproductive and somatic cell numbers in diverse *Volvox* (Chlorophyta) species. *Evol. Ecol. Res.* **14** 707–727

Shin T, Kraemer D, Pryor J, Liu L, Rugila J, Howe L, Buck S, Murphy K, *et al*. 2002 A cat cloned by nuclear transplantation. *Nature* **415** 859

Shomron N 2010 MicroRNAs and developmental robustness: a new layer is revealed. *PLoS Biol.* **8** e1000397

Shushu DD, Comar JM and Abegaz BM 2009 Somaclonal variation in *in vitro* regenerated *Ledebouria graminifolia* (Hyacinthaceae), an indigenous bulb in Botswana and its potential exploitation as an ornamental plant. *J. Biol. Sci.* **9** 152–158

Simons BD and Clevers H 2011 Strategies for homeostatic stem cell self-renewal in adult tissues. *Cell* **145** 851–862

Simpson SJ, Sword GA and Lo N 2011 Polyphenism in insects. *Curr. Biol.* **21** R738–749

Singh GP 2013 Coupling between noise and plasticity in *E. coli. G3 Genes Genomes Genet.* **32** 2115–2120

Singh A and Weinberger LS 2009 Stochastic gene expression as a molecular switch for viral latency. *Curr. Opin. Microbiol.* **12** 460–466

Skinner MK, Manikkam M, Haque MM, Zhang B and Savenkova MI 2012 Epigenetic transgenerational inheritance of somatic transcriptomes and epigenetic control regions. *Genome Biol.* **13** R91

Skirvin RM, McPheeters KD and Norton M 1994 Sources and frequency of somaclonal variation. *HortScience* **29** 1232–1237

Smith LC and Murphy BD 2004 Genetic and epigenetic aspects of cloning and potential effects on offspring of cloned mammals. *Clon. Stem Cells* **6** 126–132

Smith MS, Milton I and Strand MR 2010 Phenotypically plastic traits regulate caste formation and soldier function in polyembryonic wasps. *J. Evol. Biol.* **23** 2677–2684

Smith EA, Collette SB, Boynton TA, Lillrose T, Stevens MR, Bekker MF, Eggett E and St Clair SB 2011 Developmental contributions to phenotypic variation in functional leaf traits within quaking aspen clones. *Tree Physiol.* **31** 68–77

Smits WK, Kuipers OP and Veening J-W 2006 Phenotypic variation in bacteria: the role of feedback regulation. *Nat. Rev. Microbiol.* **4** 259–271

Sozzani R and Benfey PN 2011 High-throughput phenotyping of multicellular organisms: finding the link between genotype and phenotype. *Genome Biol.* **12** 219

Spiller DG, Wood CD, Rand DA and White MRH 2010 Measurement of single-cell dynamics. *Nature* **465** 736–745

Spratt BG 2004 Exploring the concept of clonality in bacteria. *Meth. Mol. Biol.* **266** 323–352

Spudich JL and Koshland DE Jr 1976 Non-genetic individuality: chance in the single cell. *Nature* **262** 467–471

Srinivasan DG and Brisson JA 2012 Aphids: a model for polyphenism and epigenetics. *Genet. Res. Intern.* **2012** 431–531

Stamps J and Groothuis TGG 2010 The development of animal personality: relevance, concepts and perspectives. *Biol. Rev.* **85** 301–325

Starrfelt J and Kokko H 2012 Bet-hedging – a triple trade-off between means, variances and correlations. *Biol. Rev.* **87** 742–755

Stewart-Savage J, Wagstaff BJ and Yund PO 1999 Developmental basis of phenotypic variation in egg production in a colonial ascidian: primary oocyte production *versus* oocyte development. *Biol. Bull.* **196** 63–69

Storrs EE and Williams RJ 1968 A study of monozygous quadruplet armadillos in relation to mammalian inheritance. *Proc. Natl. Acad. Sci. USA* **60** 910–914

Suomalainen E, Saura A and Lokki J 1987 *Cytology and evolution in parthenogenesis* (Boca Raton: CRC Press)

Takahashi KH, Rako L, Takano-Shimizu T, Hoffmann AA and Lee SF 2010 Effects of small Hsp genes on developmental stability and microenvironmental canalization. *BMC Evol. Biol.* **10** 284

Taylor JS and Raes J 2004 Duplication and divergence: the evolution of new genes and old ideas. *Annu. Rev. Genet.* **38** 615–643

Taylor JW, Jacobson DJ and Fisher MC 1999 The evolution of asexual fungi: reproduction, speciation and classification. *Annu. Rev. Phytopathol.* **37** 197–246

Thattai M and van Oudenaarden A 2001 Intrinsic noise in gene regulatory networks. *PNAS* **98** 8614–8619

Thattai M and van Oudenaarden A 2004 Stochastic gene expression in fluctuating environments. *Genetics* **167** 523–530

The 1000 Genomes Project Consortium 2010 A map of human genome variation from population-scale sequencing. *Nature* **467** 1061–1073

Tibayrenc M and Ayala FJ 2012 Reproductive clonality of pathogens: a perspective on pathogenic viruses, bacteria, fungi, and parasitic protozoa. *PNAS* **109** E3305–3313

Tordoff MG, Bachmanov AA and Reed DR 2007a Forty mouse strain survey of water and sodium intake. *Physiol. Behav.* **91** 620–631

Tordoff MG, Bachmanov AA and Reed DR 2007b Forty mouse strain survey of voluntary calcium intake, blood calcium, and bone mineral content. *Physiol. Behav.* **91** 632–643

Trillmich F and Hudson R 2011 The emergence of personality in animals: the need for a developmental approach. *Dev. Psychobiol.* **53** 505–509

Tsuru S, Ichinose J, Kashiwagi A, Ying B-W, Kaneko K and Yomo T 2009 Noisy cell growth rate leads to fluctuating protein concentration in bacteria. *Phys. Biol.* **6** 036015

Tsutsui ND, Suarez AV, Holway DA and Case TJ 2000 Reduced genetic variation and the success of an invasive species. *PNAS* **97** 5948–5953

Turing AM 1952 The chemical basis of morphogenesis. *Phil. Trans. R. Soc. B* **237** 37–72

Turkheimer E and Waldron M 2000 Nonshared environment: a theoretical, methodological, and quantitative review. *Psychol. Bull.* **126** 78–108

Turck F and Coupland G 2014 Natural variation in epigenetic gene regulation and its effects on plant developmental traits. *Evolution* **68** 620–631

Turko AJ, Earley RL and Wright PA 2011 Behaviour drives morphology: voluntary emersion patterns shape gill structure in genetically identical mangrove rivulus. *Anim. Behav.* **82** 39–47

Uyttewaal M, Burian A, Alim K, Landrein B, Borowska-Wykręt D, Dedieu A, Peaucelle A, Ludynia M, *et al*. 2012 Mechanical stress acts via katanin to amplify differences in growth rate between adjacent cells in *Arabidopsis. Cell* **149** 439–451

Van Praag H, Kempermann G and Gage FH 2000 Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* **1** 191–195

Van Valen L 1962 A study of fluctuating asymmetry. *Evolution* **16** 125–142

Veening J-W, Smits WK and Kuipers OP 2008 Bistability, epigenetics and bet-hedging in bacteria. *Annu. Rev. Microbiol.* **62** 193–210

Veitia RA 2005 Stochasticity or the fatal 'imperfection' of cloning. *J. Biosci.* **30** 21–30

Verhoeven KJF and Preite V 2014 Epigenetic variation in asexually reproducing organisms. *Evolution* **68** 644–655

Verstrepen KJ and Fink GR 2009 Genetic and epigenetic mechanisms underlying cell-surface variability in Protozoa and Fungi. *Annu. Rev. Genet.* **43** 1–24

Vickaryous MK and Hall BK 2006 Human cell type diversity, evolution, development, and classification with special reference to cells derived from the neural crest. *Biol. Rev.* **81** 425–455

Vinck A, Terlou M, Pestman WR, Martens EP, Ram AF, van den Hondel CAMJJ and Wösten HAB 2005 Hyphal differentiation in the exploring mycelium of *Aspergillus niger*. *Mol. Microbiol.* **58** 693–699

Viney M and Reece SE 2013 Adaptive noise. *Proc. R. Soc. B* **280** 20131104

Vogt G 2007 Exposure of the eggs to 17α-methyl testosterone reduced hatching success and growth and elicited teratogenic effects in postembryonic life stages of crayfish. *Aquat. Toxicol.* **85** 291–296

Vogt G 2008 The marbled crayfish: a new model organism for research on development, epigenetics and evolutionary biology. *J. Zool.* **276** 1–13

Vogt G 2010 Suitability of the clonal marbled crayfish for biogerontological research: a review and perspective, with remarks on some further crustaceans. *Biogerontol.* **11** 643–669

Vogt G 2011 Marmorkrebs: natural crayfish clone as emerging model for various biological disciplines. *J. Biosci.* **36** 377–382

Vogt G 2012 Hidden treasures in stem cells of indeterminately growing bilaterian invertebrates. *Stem Cell Rev. Rep.* **8** 305–317

Vogt G 2015 Research on stem cells, aging, cancer resistance, and epigenetics in marbled crayfish and relatives: potential benefits for human biology and medicine; in *Freshwater crayfish: global overview* (eds) T Kawai, Z Faulkes and G Scholtz (Boca Raton: CRC Press) pp 115–157

Vogt G and Rug M 1999 Life stages and tentative life cycle of *Psorospermium haeckeli*, a species of the novel DRIPs clade from the animal-fungal dichotomy. *J. Exp. Zool.* **283** 31–42

Vogt G, Tolley L and Scholtz G 2004 Life stages and reproductive components of the Marmorkrebs (marbled crayfish), the first parthenogenetic decapod crustacean. *J. Morphol.* **261** 286–311

Vogt G, Huber M, Thiemann M, van den Boogaart G, Schmitz OJ and Schubart CD 2008 Production of different phenotypes from the same genotype in the same environment by developmental variation. *J. Exp. Biol.* **211** 510–523

Vogt G, Wirkner CS and Richter S 2009 Symmetry variation in the heart-descending artery system of the parthenogenetic marbled crayfish. *J. Morphol.* **270** 221–226

Vogt G, Raddatz G, Falckenhayn C, Hanna K, Musch T and Lyko F 2013 Ökologische Anpassung invasiver Arten durch epigenetische Mechanismen: ein Teilaspekt des Marmorkrebs-Projekts am Deutschen Krebsforschungszentrum Heidelberg, in *Internationale Flusskrebstagung* (Schleiden-Gemünd: Biologische Station StädteRegion Aachen) pp 109–113

Vrijenhoek RC 1998 Animal clones and diversity: are natural clones generalists or specialists? *BioScience* **48** 617–628

Waddington CH 1942 Canalization of development and the inheritance of acquired characters. *Nature* **150** 563–565

Waddington CH 1953 Genetic assimilation of an acquired character. *Evolution* **7** 118–126

Waddington CH 1957 *The strategy of the genes: a discussion of some aspects of theoretical biology* (London: Gorge Allen and Unwin)

Wagner GP, Pavlicev M and Cheverud JM 2007 The road to modularity. *Nat. Rev. Genet.* **8** 921–931

Walsh TK, Brisson JA, Robertson HM, Gordon K, Jaubert-Possamai S, Tagu D and Edwards OR 2010 A functional DNA methylation system in the pea aphid, *Acyrthosiphon pisum. Insect Mol. Biol.* **19** 215–228

Wang D and Bodovitz S 2010 Single cell analysis: the new frontier in 'omics'. *Trends Biotechnol.* **28** 281–290

Wang Z and Zhang J 2011 Impact of gene expression noise on organismal fitness and the efficacy of natural selection. *PNAS* **108** E67–76

Wang G-Z, Lercher MJ and Hurst LD 2011 Transcriptional coupling of neighboring genes and gene expression noise: evidence that gene orientation and noncoding transcripts are modulators of noise. *Genome Biol. Evol.* **3** 320–331

Warren E 1899 An observation on inheritance in parthenogenesis. *Proc. R. Soc.* **65** 154–158

Warren E 1902 Variation and inheritance in the parthenogenetic generations of the aphis *Hyalopterus trirhodus* (Walker). *Biometrika* **1** 129–154

Weigel D and Colot V 2012 Epialleles in plant evolution. *Genome Biol.* **13** 249

West-Eberhard MJ 2003 *Developmental plasticity and evolution* (New York: Oxford University Press)

Williams RJ and Pelton RB 1966 Individuality in nutrition: effects of vitamin A-deficient and other deficient diets on experimental animals. *Proc. Natl. Acad. Sci. USA* **55** 126–134

Wilson EO 1975 *Sociobiology: the new synthesis* (Cambridge: Harvard University Press)

Wilson J 1999 *Biological individuality: the identity and persistence of living entities* (Cambridge: Cambridge University Press)

Wilson R 2007 The biological notion of individual; in *Stanford Encyclopedia of Philosophy* (Stanford: Center for the Study of Language and Information, Stanford University)

Woese CR, Kandler O and Wheelis ML 1990 Towards a natural system of organisms: proposal for the domains Archaea, Bacteria, and Eucarya. *Proc. Natl. Acad. Sci. USA* **87** 4576–4579

Woods HA 2014 Mosaic physiology from developmental noise: within-organism physiological diversity as an alternative to phenotypic plasticity and phenotypic flexibility. *J. Exp. Biol.* **217** 35–45

Woolff CM 1997 Does the genotype for schizophrenia often remain unexpressed because of canalization and stochastic events during development? *Psychol. Med.* **27** 659–668

Wright S 1920 The relative importance of heredity and environment in determining the piebald pattern of guinea-pigs. *Proc. Natl. Acad. Sci. USA* **6** 320–332

Wright S and Chase HB 1936 On the genetics of the spotted pattern of the guinea pig. *Genetics* **21** 758–787

Xia J, Han L and Zhao Z 2012 Investigating the relationship of DNA methylation with mutation rate and allele frequency in the human genome. *BMC Genomics* **13** S7

Yang B-C, Lee S-H, Hwang S, Lee H-C, Im G-S, Kim D-H, Lee D-K, Lee K-T, *et al*. 2012 Phenotypic characterization of Hanwoo (native Korean cattle) cloned from somatic cells of a single adult. *BMB Rep.* **45** 38–43

Yvert G 2014 'Particle genetics': treating every cell as unique. *Trends Genet.* **30** 49–56

Yvert G, Ohnuki S, Nogami S, Imanaga Y, Fehrmann S, Schacherer J and Ohya Y 2013 Single-cell phenomics reveals intra-species variation of phenotypic noise in yeast. *BMC Syst. Biol.* **7** 54

Zhang Z, Qian W and Zhang J 2009 Positive selection for elevated gene expression noise in yeast. *Mol. Syst. Biol.* **5** 299

Zhang Y-Y, Fischer M, Colot V and Bossdorf O 2013 Epigenetic variation creates potential for evolution of plant phenotypic plasticity. *New Phytol.* **197** 314–322

Zhu S and Chen H 1995 Megascopic multicellular organisms from the 1700-million-year-old Tuanshanzi Formation in the Jixian area, north China. *Science* **270** 620–622

Zhurov V, Terzin T and Grbić M 2004 Early blastomere determines embryo proliferation and caste fate in a polyembryonic wasp. *Nature* **432** 764–769

Zordan RE, Galgoczy DJ and Johnson AD 2006 Epigenetic properties of white-opaque switching in *Candida albicans* are based on a self-sustaining transcriptional feedback loop. *PNAS* **103** 12807–12812

Zou X, Ma W, Solov'yov IA, Chipot C and Schulten K 2012 Recognition of methylated DNA through methyl-CpG binding domain proteins. *Nucl. Acids Res.* **40** 2747–2758

MS received 02 January 2014; accepted 19 January 2015

Corresponding editor: SUBHASH C LAKHOTIA