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# Commentary: The presence of bifurcations as a 'third component of individual differences': implications for quantitative (behaviour) genetics

**Kees-Jan Kan,[1,2]* Dorret I Boomsma,[1] Conor V Dolan[1,2] and Han LJ van der Maas[2]**

[1]Department of Biological Psychology, Free University, Amsterdam, The Netherlands and [2]Department of Psychological Methods, University of Amsterdam, Amsterdam, The Netherlands

*Corresponding author. Biological Psychology, VU University, Amsterdam, 1018 WB, The Netherlands. E-mail: k.j.kan@vu.nl

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Why is Gärtner's paper[1] so interesting? It is for a number of reasons, but the most interesting is not the finding that phenotypic differences among animals still exist after standardization of genotype and environment (described in the first part of Gärtner's paper). These differences are expected to remain to a certain extent, because complete experimental control is impossible. More interesting is how large these differences are. Particularly interesting are the results of Gärtner's experiments in which he attempts to alter the amount of phenotypic variance by varying the amount of variance in environmental conditions and genetic influences (described in the second part). These results suggested the presence of an additional source of phenotypic variance besides the genotype and environment. Long before Gärtner's paper had been published, various researchers had speculated about the existence of such non-genetic, non-environmental ('third') source of variance. These included pioneering geneticists such as Sewall Wright (see the first path diagram ever[2]), Sir Kenneth Mather and Jinks[3] (p. 6) and Douglas Falconer and Mackay[4] (p. 135). As we argue below, whereas this third source of variance was demonstrated in experimental organisms, it is also relevant to the interpretation of human quantitative (behaviour) genetic results (see also previous research[5–8]).

## Evidence for a third component of phenotypic differences

In quantitative genetic modelling, the phenotype is determined by two factors: the genotype and the environment.[4,9] According to Falconer and Mackay[4] (p. 108), '[w]e may think of genotype conferring a certain value on the individual and the environment causing a deviation of it'. They model an individual's phenotypic value or score ($P_i$) as a (linear) combination of an individual's genotypic value ($G_i$) and an environmental value ($E_i$): $P_i = G_i + E_i$, and set the population mean of $G_i$ ($E[G_i]$) equal to the mean of $P_i$ ($E[P_i]$) and that of $E_i$ ($E[E_i]$) to 0. This model can be rewritten as $P_i^* = P_i - E[P_i] = P_i - E[G_i] = G_i + E_i - E[G_i] = G_i^* + E_i$, where the means of $P_i^*$, $G_i^*$ and $E_i$ ($E[P_i^*]$, $E[G_i^*]$ and $E[E_i]$) are all zero. Like $E_i$, an individual's phenotypic value ($P_i^*$) and genotypic value ($G_i^*$) are now expressed as a deviation from the mean. This version of the model[9] accurately reflects the fact that genotypic and environmental 'differences' give rise to phenotypic 'differences', and hence to phenotypic variance. In standard statistical behaviour genetic modelling, phenotypic variance ($\sigma_p^2 = E[P_i^{*2}]$) is expressed as a linear combination of the genetic variance ($\sigma_g^2 = E[G_i^{*2}]$) and the environmental variance ($\sigma_e^2 = E[E_i^2]$). More complex models may include covariance and/or statistical interaction effects.

Multiple environmental influences can effect phenotype $P_i$ (hence $E[P_i]$, hence $P_i^*$, hence $\sigma_p^2$). The variance $\sigma_e^2$ represents the variance in all environmentally induced effects on phenotype. In quantitative genetic modelling, a distinction is made between effects of environmental influences that are assumed to make individuals similar (e.g. environmental influences that cohabiting individuals share), and those that are assumed to make them dissimilar (environmental influences that are not shared). Accordingly, $\sigma_e^2$ is decomposed into shared (or common) ($\sigma_c^2$) and non-shared (or unique) environmental variance components ($\sigma_u^2$). Genetic variance ($\sigma_c^2$) is often decomposed into additive genetic variance ($\sigma_a^2$, due to additive genetic influences) and non-additive genetic variance ($\sigma_d^2$, due to dominance and epistasis). Standardization of genotype (e.g. through inbreeding) and environment (through environmental control) serves to minimize $\sigma_g^2$ ($\sigma_a^2$ and $\sigma_d^2$) and $\sigma_c^2$, so that ideally $\sigma_p^2$ equals $\sigma_u^2$. Practically, $\sigma_u^2$ is a residual variance, which includes variance due to measurement error.[4,9]

Based on the following, Gärtner[1] showed that this residual component $\sigma_u^2$ likely includes the effects of yet another source of individual differences. To investigate the role of genetic and environmental influences on phenotype, Gärtner experimented with the amount of variance in environmental and genetic influences over samples of animal strains. The rationale was that if genetic or environmental variables have a significant effect on phenotype, a decrease (increase) in the amount of variance in these variables (hence $\sigma_e^2$ or $\sigma_g^2$) should lead to a decrease (increase) in the amount of phenotypic differences (hence in $\sigma_p^2$). In Gärtner's experiments, it became clear that varying the variance in (post-natal) environmental conditions (over samples) had surprisingly little effect on the total amount of phenotypic variance. While holding the amount of genetic variance the same across samples, differences in the amount of the variance of (post-natal) environmental

variables did not result in difference in the amount of phenotypic variance. Assuming error variance remains the same, this result suggests that (i) (post-natal) environmental variables do not explain much of the phenotypic variance and (ii) there is a source of phenotypic variance that is (a) non-genetic, (b) not part of the (post-natal) environment and (c) different from measurement error. Although Gärtner speculated about the exact nature of this additional ('third') source of variance, it has to date remained unidentified.

## On the nature of the third component

Gärtner[1] established experimentally that, after taking into account systematic sources of phenotypic variance (measured environmental variables), individual differences in isogenic animals were unpredictable. Based on this result, some researchers concluded that these differences (hence a part of the residual variance) are due to an additional source (i.e. in addition to genetic and environmental sources) that comprises the effects of stochastic or chance processes at the (sub)molecular level, which influence gene expression. Notably, 21 of the 80 papers in Google Scholar that cite Gärtner interpret the additional ('third') source in terms of stochasticity; 33 of them interpret it in the context of (molecular) epigenetic processing. Although we accept that stochastic processes constitute a source of phenotypic variance, we argue that stochasticity cannot constitute the primary explanation of Gärtner's results. Environmental variables such as food intake clearly influence molecular processes (including those that regulate gene expression). It is unclear why individual differences in molecular processing induced by environmental influences should not give rise to appreciable phenotypic individual differences, whereas individual differences in molecular processing due to stochasticity or chance should. An increase in differences in gene expression, hence in phenotypic variance, is expected when the variance in environmental conditions is increased. However, as established by Gärtner, an increase in the variance of environmental variables had no significant impact on the amount of phenotypic variance. Moreover, as some[10] have rightly pointed out, chance might only be a label for the lack of knowledge about the underlying processes.

We believe that Molenaar *et al*.[5] gave a better explanation (for a similar point of view, see Turkheimer[11]). They argue that the nature of the third source is deterministic (which is not to say they exclude the presence of chance or stochastic processes):

> Developmental differences can be generated by three kinds of sources: genetical, environmental and epigenetical. The latter epigenetical influences are the result of autonomous developmental processes with emergent selforganizing properties and obeying non-linear dynamics. The structure of such autonomous developmental processes can be represented by non-linear reaction-diffusion systems or non-linear deterministic systems of differential equations. The structure of each developmental mechanism, in particular the parameters in the corresponding non-linear model system, will be determined by genetical and environmental influences and hence will vary between subjects.[5] (p. 521)

Key is that an organism is regarded as the outcome of a dynamical system, and that the system's dynamics are non-linear.

In contrast to a linear system, a non-linear dynamical system is characterized by a disproportional relationship between cause and effect.[12] This implies that, depending on the system's developmental state, at some points in development large influences have small or limited effects, whereas at other points in development even small influences can have large effects. Hence, near indistinguishable sets of initial conditions or perturbations at critical moments may produce very different outcomes. In addition, the outcome of a non-linear system may be hard to predict, even if any form of stochasticity is absent. In other words, the outcome will appear stochastic despite the fact that the system is deterministic. The unpredictability arises from the lack of precise knowledge concerning the conditions.

Only few of the papers that cite Gärtner[1] interpret his results explicitly in terms of non-linearity.[5,8,13] A few other papers link Gärtners results to non-linear development implicitly.[14–16] We believe Gärtner provided evidence that is consistent with the presence of non-linear development. First, he described that large (post-natal) environmental influences had small or limited effects on individual differences in the biological traits, whereas small influences during very early pre-natal stages of development had large effects. So the relationship between causes and effects was indeed disproportional, and the systems (i.e. the animals) were sensitive to initial conditions. Second, the outcome was unpredictable and appeared stochastic.

In the light of the discussion of the nature of the third source, it is important to note that non-linear effects can accumulate and combine in different ways. They can amplify each other, as they do in chaotic systems, or they can average out to produce a kind of statistical macro-level behaviour (which may show sudden shifts known as bifurcations). Eaves *et al*.[6] (p. 47) argued that 'although ''chaos'' may be an important element in development, its effects may not be universal, otherwise the developmental data would appear differently', meaning that in chaotic systems the genetic structure initially present will be

destroyed and twin correlations will approach zero, so that estimated heritabilities will approach zero,[7] which is not frequently observed in behaviour genetic studies. We propose that although lower-level processes (e.g. molecular epigenetic processes) likely involve chaotic behaviour, certain higher-level outcomes of these processes (e.g. brain size or intelligence) are 'averaged-out outcomes'. The development of these outcomes may show only a small number of bifurcations (phase or stage transitions), if any at all, so that the genetic structure (and so the heritability, based on the twin correlations) is better preserved.

The results of simulation experiments support this line of reasoning. Kan *et al.*[8] modelled individual differences in non-linear (but non-chaotic) neural network development. The model had been used previously to investigate the effects of the coupling between activity-dependent neurite outgrowth and inhibition.[17] This combination can account for multiple developmental pathways to multiple stable end states, which can be associated with developmental pathways to normal and pathological outcomes.[17] In the simulations of Kan *et al.*,[8] variance in the parameters (the underlying causes of the phenotypic traits, hence of normal or pathological outcome) was due to both genetic and environmental influences. Non-shared influences accounted for 1% of the variance in the total (genetic and environmental) influences, shared environmental influences for 49% and genetic influences for 50%. During the course of (non-chaotic) development of neural connection strength, twin correlations were preserved, but better in monozygotic twins than in dizygotic twins, meaning that initial high monozygotic twin correlations remained relatively stable, whereas lower (but substantial) dizygotic twin correlations decreased (although not to values close to 0). After systems were fully developed, when bifurcations were present, the genetic component accounted for about two-thirds of the variance, and the (non-shared) environmental component for the remaining one-third. As a result of this non-linear development, the effects of shared environmental influences became undetectable; no variance was attributed to the shared component. When bifurcations were absent, the variance components were estimated correctly (and shared influences were detectable).

In line with Molenaar *et al.*,[5] Kan *et al.*[8] concluded that, although the ultimate influences on phenotype are only genetic and environmental, the presence of bifurcations (which is a necessary but insufficient condition for the presence of chaos) constituted an independent third source of phenotypic variance (Figure 1).

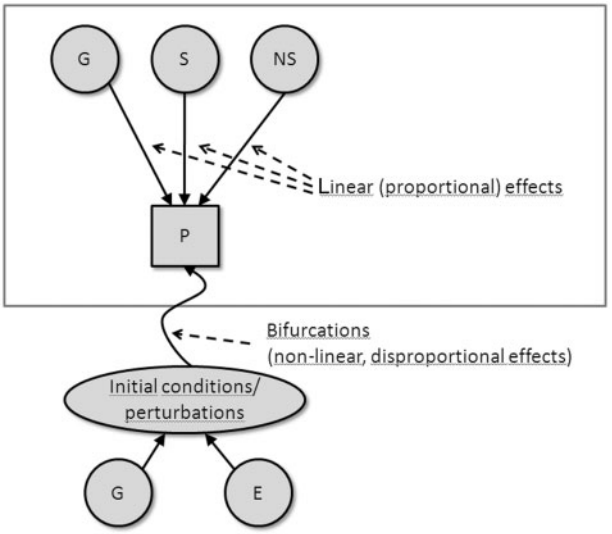


**Figure 1** Phenotype (P) as a function of linearly and non-linearly acting genetic and environmental influences. In linear behaviour genetic modelling, the effects of environmental influences are divided into components, which should reflect the effects of shared (S) and non-shared (NS) environmental influences. In statistical analyses, the NS component will subsume error variance. Since bifurcating processes (possibly leading to chaos) will have unsystematic (disproportional) effects, which are difficult to distinguish from error, the NS component will also contain their effects. The true genetic (G) and environmental (E) influences on initial conditions or perturbations will be hard to detect. Although the ultimate influences on phenotype are only genetic and environmental, the presence of bifurcations constitutes a distinct and independent source of variance

## Implications

The results of the simulations of Eaves *et al.*,[6] Molenaar and Raijmakers,[7] and Kan *et al.*[8] are in line with Gärtner's[1] experimental results. If bifurcations are present, standardization of genotype and environment leads to a situation in which most phenotypic variance is due to this source of variance. The variance will be difficult to distinguish from variance due to error or stochasticity, because the relationship between cause and effect will appear unsystematic. In addition, depending on the developmental stage, alteration of the variance in environmental influences may or may not have an effect on the total variance. Hence, cloning (introducing extra environmental influences as compared with not cloning) may increase phenotypic variance significantly, whereas increasing the variance in post-natal influences may have little effect. It implies that phenotypic variance in isogenic animals that are held under identical post-natal conditions can be higher than in genetically heterogeneous animals that are raised in natural settings.

The results of Kan *et al.*[8] are also consistent with certain results in developmental behaviour genetic studies, for example, studies of intelligence (i.e. individual differences in cognition). These results can be summarized as follows.[18–20]

- A substantial amount of phenotypic variance can be attributed to genetic differences.
- A substantial amount of phenotypic variance can be attributed to non-shared environmental influences.
- In the whole population, shared environmental variance is usually substantially smaller than the genetic variance.
- In many psychological traits, the relative contributions of the shared component and non-shared component change throughout development: shared environmentability decreases, often down to values close to zero. Hence, ultimately, most of the environmental variance is attributed to the non-shared environmental component.
- In intelligence, throughout development heritability increases (and environmentability decreases).

The consequences of the presence of bifurcations may be far-reaching. For example, the increase of heritability and the decrease of the relative contribution of common environmental variance in intelligence is usually explained as the result of an increase in genotype–environment correlation.[9,20] An additional or alternative explanation is thus that these changes can also be attributed to the presence of bifurcations in cognitive development. Also, the exact influences on initial conditions or perturbations at critical moments will be generally untraceable in standard behaviour genetic modelling (of twin data, say), because the effects are disproportional to their causes. This is consistent with the fact that to date the search for specific environmental and genetic influences on many behavioural traits (including intelligence) has met with limited success.[21,22] Moreover, because the effects of the presence of bifurcations may result in changes in the estimated environmental and genetic variance over time, investigators might be inclined to seek explanations in terms of changing environmental factors, genetic factors or gene–environment correlation, whereas the ultimate causes lie elsewhere. Or researchers may assume the presence of genetic interaction effects such as dominance or epistasis, whereas these may be absent.

A possible step researchers may take to investigate whether non-linear (bifurcating, possibly chaotic) developmental processes contribute to variance in a trait, is to study the developmental trajectory of that trait. The presence of critical periods or stage transitions strongly suggest that the process is non-linear. Van der Maas and Molenaar[23] discuss in considerable detail the detection and the classification of stage transitions and the ways to distinguish between mere acceleration in growth (e.g. growth spurts) and transitions due to non-linear dynamics.

The role of non-linear development, as found by Gärtner[1], thus provides a challenging perspective on the sources of individual differences and the interpretation of variance components. Adopting a non-linear dynamical systems perspective may bridge the gap between developmental theories of individual differences and (linear) statistical modelling.

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# Commentary: Ageing—what's all the noise about? Developments after Gärtner

**Thomas BL Kirkwood**

Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne NE4 5PL, UK. E-mail: tom.kirkwood@ncl.ac.uk

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It would be possible but mistaken to presuppose a message of regret in Gärtner's[1] account of 'the limited success of a 30 year long effort to standardize laboratory animals'. Thirty years is three-quarters of the typical career and the outcome might seem like failure. However, in the spirit of Isaac Asimov's oft-quoted remark 'The most exciting phrase to hear in science, the one that heralds new discoveries, is not ''Eureka!'' (I've found it!), but ''That's funny . . .'' ', the report of 'a third component causing random variability beside environment and genotype' was an exciting milestone. For Caleb Finch and me, coming across Gärtner's paper during the final stages of writing our book *Chance, Development and Ageing*[2] was welcome confirmation that someone before us was thinking along similar lines. In our case, we were interested in the extensive stochastic variation manifest in ageing, which seems not to be explicable in terms of the usual dichotomy between genes and environment. The commonplace dismissal that everything which is not 'genetic' should be counted as 'environmental' makes little sense when confronted with the fact that within an isogenic population of nematode worms (*Caenorhabditis elegans*) raised in extremely uniform conditions (even to the extent of stirred liquid cultures), individuals show enormous variation in lifespan. This variation is all the more striking because the worms' development is so exceptionally reproducible, each worm reaching adulthood in uniform time and with exactly 959 somatic cells. Of course, genes can alter worm lifespan, as does environment (e.g. temperature), but the variance in populations of extended-lifespan mutants and wild-type worms was such that the lifespan distributions showed extensive overlap in spite of a large difference in mean.[3]

Since Gärtner's publication, much has been learnt about the noise that operates at all levels within the organisms. Phelan and Austad[4] confirmed that often in laboratory studies of animal models of ageing, inbred strains exhibit less uniformity than $F_1$ hybrids. Random variability affects how molecules diffuse and interact, how cell numbers in different organs vary through random effects on cell fates and how cells accumulate errors and damage.[3] At the deepest level—that of the molecular interactions that govern gene expression—it is clear that substantial intracellular 'noise' is seen in protein production, which appears to be dominated by stochastic effects within the machinery for producing and destroying the messenger RNAs. Furthermore, some of this noise seems actually beneficial in helping to enhance the ways that molecular systems can detect and respond to internal signals.[5] The intrinsic hypermutability that acts within the immune system to generate capacity to recognize novel antigens is another instance of noise