Life's dual nature: a way out of the impasse of the gene-centred 'versus' complex systems controversy on life

Published in: Pontarotti P (ed) (2015) Evolutionary Biology: Biodiversification from Genotype to Phenotype. Springer, Berlin-Heidelberg, pp. 35-52

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Abstract: Living cells and organisms are complex physical systems. Does their organization or complexity primarily rely on the intra-molecular crystalline structure of genetic nucleic acid sequences? Or is it, as critics of the 'gene-centred' perspective claim, predominantly a result of the inter- and supra-molecular – thus 'holistic' – network dynamics of genetic and various extra-genetic factors? The twentieth-century successes in several branches of genetics caused intensive focus on the causal role of genes in the biochemistry, development and evolution of living organisms, resulting in a relative abstraction or even neglect of life's complex systems dynamics. Today, however, partly due to the success of systems biology, a number of authors defend life's systems complexity while criticizing the gene-centred approach. Here, we offer a way out of the impasse of the gene-centred 'versus' complex systems perspective to arrive at a more balanced and complete understanding of life's multifaceted nature. After sketching the conceptual and historical background of the controversy, we show how the present state of knowledge in biology vindicates both the holistically complex and gene-centred nature of life on Earth, but decisively falsifies extreme genetic 'determinism' and 'reductionism' as well as extreme 'gene-de-centrism'. Contrary to what is often claimed, the fact that genes are one among many extra-genetic causal factors contributing to the biochemistry and development of cells and organisms, only undermines or falsifies genetic determinism and reductionism but not necessarily gene-centrism. Some implications for evolutionary theory, i.e., for the controversy between the Modern Synthesis and an 'Extended Synthesis', are outlined.

1. Introduction and chapter outline

During the first half of the twentieth century, some biological disciplines, like classical and population genetics, were inevitably gene-centred, whereas others, like developmental biology and/or embryology, were more focussed on life's holistic complexity. The spectacular advances in molecular biology and genetics during the second half of the twentieth century, however, caused intensive focus on the causal role of genes in the biochemistry, development and evolution of living organisms. This strong emphasis on genetic causation was at the cost of a clear understanding of life's holistic network dynamics (Gilbert and Sarkar 2000). As

'reductionism' flourished, there even was an unwillingness to recognize the latter aspect of life, with Conrad Waddington (1957) being a notable exception of this trend. Today, we see an opposite tendency: due to the success of systems biology the focus is on dynamic *network complexity*. Some authors (e.g., Goodwin 1984, 1994; Oyama 1985; Oyama et al. 2001; Keller 2000; Moss 2003; Callebaut et al. 2007; Noble 2008, 2010, 2012; Noble et al. 2014) have been defending life's holistic systems complexity while denying gene-centeredness as a property of life. The present chapter's objective is to end the swinging of the pendulum from one extreme to the other, as recognizing just one of life's characteristics *at the cost* of another one seriously stands in the way of a more balanced and complete understanding of life's *multifaceted nature*. Life is constituted by *inter- and supra-molecular* or holistic network dynamics which is, however, *permeated* by functional gene products (i.e., functional RNAs and proteins) and hence by genetic sequence information derived from the *intra-molecular crystalline* structure of nucleic acid sequences. Both characteristics, holistic complexity and gene-centeredness, are *essential* to a clear understanding of the nature of life on Earth.

In section 2, we further sketch the conceptual and historical background of the controversy. In section 3, we demonstrate how the present state of knowledge in biology vindicates both life's holistically complex and gene-centred nature, but at the same time falsifies extreme genetic 'determinism' and 'reductionism' (according to which biochemical, cellular and organismal organization are quasi-exhaustively determined by and reducible to genetic sequence information)[1] as well as extreme 'gene-de-centrism' (according to which genes are quasi-entirely 'de-centralized' and/or 'relativized' within the complex biochemical and developmental dynamics of cells and organisms). We show, among others, that the fact that genes are one among many extra-genetic causal factors contributing to the biochemistry and development of cells and organisms (cf. Oyama et al. 2001; Jablonka and Lamb 2005; Noble 2008, 2010, 2012; De Tiège et al. 2014; Noble et al. 2014), only undermines or falsifies genetic determinism and reductionism but not gene-centrism. In section 4, we conclude with some implications for evolutionary theory, i.e., for the controversy between the Modern Synthesis and a so-called 'Extended Synthesis' (e.g., Pigliucci and Müller 2010; Noble et al. 2014; Laland et al. 2014).

2. Conceptual and historical background of the controversy

A number of biological research disciplines, such as classical, population, molecular and developmental genetics, are gene-centred in the sense that their conceptual and methodological research framework is centred on the concept of the gene. Their 'methodological gene-centrism', however, can be contrasted with the 'meta-biological' perspective that life is also in essence a gene-centred phenomenon or process, a position that could be termed 'ontological gene-centrism'.[2] Both methodological and ontological gene-centrism reinforced each other during the course of twentieth-century biology. Research successes in methodologically gene-centred disciplines like classical, population and molecular genetics reinforced the belief in life's gene-centred nature (i.e., ontological gene-centrism) and, vice versa, theoretical accounts on life's ontologically gene-centred foundation (e.g., Muller 1922, 1966; Schrödinger 1944; Dawkins 1976) catalysed the development of methodologically gene-centred disciplines such as population genetics, molecular genetics and gene-selectionism.

[1] The idea that gene-centrism should be distinguished from genetic determinism and reductionism has already been put forward by one of us (Tanghe 2013) and even goes back to Dawkins (1982).

[2] A distinction between methodological and ontological gene-centrism was already made by Thange (2013, pp. 294-295).

The idea of the gene/genome as the 'central (re)source' of order in cells and organisms (ontological gene-centrism) can be traced back to August Weismann's (1889, 1893, 1904) thesis – later dubbed the 'Weismann barrier' – which stated that structural specifications or instructions can be transferred from germ-plasm to soma-plasm but not the other way around (for more details, see Mayr 1982; Gould 2002; Haig 2007; Tanghe 2013; De Tiège et al. 2014). A few decades later, the geneticist Hermann J. Muller (1922, p. 32) wrote in his "Variation Due to Change in the Individual Gene" that "genes exist as ultramicroscopic particles", that "their influences nevertheless permeate the entire cell", that "they play a fundamental role in determining the nature of all cell substances, cell structures, and cell activities", and that "through these cell effects, in turn, the genes affect the entire organism". Muller's ideas on the *centrality of the gene in life* were backed up by his research on X-ray-induced genetic mutations causing changes in the biochemistry and development of cells and organisms (i.e., gene-centrism at the proximate-physical-biochemical-physiological-developmental level) which can, thereafter, be transgenerationally inherited and subjected to natural selection (i.e., gene-centrism at the ultimate-evolutionary level). His views were highly influential on the rise of both population genetics and molecular biology and genetics (Witkin 2001). They also indirectly – via biophysicist Max Delbrück – inspired quantum physicist Erwin Schrödinger (1944) to identify the gene as an 'aperiodic crystal', i.e., as an 'equilibrium structure' characterized by a low statistical entropy and held together by the strong chemical (covalent) bond. Schrödinger argued that the aperiodically crystalline genetic material is the main negentropic and/or 'informational' contributor to cellular and organismal organization, allowing the latter to metabolize and develop resources into ordered biomass – a process he termed 'order from disorder' (cf. gene-centrism at the proximate-physical-biochemical-physiological-developmental level). This intra-generational process was contrasted with the inter-generational process of 'order from order', meaning cellular and organismal reproduction underpinned by the replication of the genetic material (cf. gene-centrism at the ultimate-evolutionary level). Schrödinger's book further catalysed the gene-centred direction taken by post-war molecular biology and biology in general (Olby 1974; Morange 1998; Keller 2000; Moss 2003). It was, among others, influential on Francis Crick's (1958, 1970) 'central dogma' of molecular biology, a somewhat 'molecularized' version of the Weismann barrier, which states that genetic sequence-specificity or information cannot pass from protein to protein nor from protein 'backwards' to nucleic acid (DNA/RNA).[3] The development of gene-centrism through the work of Weismann, Muller, Schrödinger, Crick and others resulted in the understanding of the gene/genome as a kind of 'central source' (Griesemer 2002, 2005) or 'ROM-device' (Shapiro 2011, 2013) from which there is a quasi-unidirectional flow of order, negentropy and/or information into cellular biochemistry and development.

Gene-centrism, which is centred on the *intra-molecular crystalline* structure of genetic nucleic acid sequences, can be contrasted with a more holistic complex systems perspective on life, emphasizing the *inter- and supra-molecular* – thus holistic – network dynamics of many molecular species of which nucleic acids are one of them. Here too, the distinction can be made between a 'methodological holism/complexity', exemplified by disciplines such as pre-war embryology and present-day systems biology, and the 'ontological holism/complexity' that is argued for by more theoretically and meta-biologically inclined biologists interested in the very nature of life, such as Brian Goodwin (1984, 1994) and Stuart

[3] The central dogma is derived from some mechanically implausible if not impossible transfers of linear sequence information. Sequence information can be transferred between DNA- and RNA-sequences (transcription and reverse transcription) and from DNA/RNA-sequences to amino acid sequences (translation), but not from amino acid sequences to nucleic acid sequences (no reverse translation), nor from 3D protein to either protein or nucleic acid.

Kauffman (1993, 1995, 2000). From the 1980s onwards, these and other theorists (e.g., Oyama 1985; Oyama et al. 2001; Gilbert and Sarkar 2000; Keller 2000; Van Speybroeck 2000; Griesemer 2002; Moss 2003; Jablonka and Lamb 2005; Stotz 2006a,b; Callebaut et al. 2007; Shapiro 2009, 2011, 2013; Noble 2008, 2010, 2011, 2012; Griffiths and Stotz 2013; De Tiège et al. 2014; Noble et al. 2014) have been criticizing the 'reductionist' gene-centred orthodoxy of reducing the complex inter- and supra-molecular organization of cells and organisms to the intra-molecular order of just one class of molecules – nucleic acid sequences. The gene-centred orthodoxy sees the structure of genetic nucleic acid sequences as the primary or main (re)source of order in cellular and organismal organization, while the complex systems perspective casts genes as 'one among many resources' within the collective inter- and supra-molecular dynamics or self-organization responsible for cellular and organismal organization. That is, the latter perspective pleads for a profound 'contextualization', and perhaps even a 'de-centralization', of the gene within the inter- and supra-molecular dynamics of cells and organisms as complex systems. As Kauffman (1995, p. 83; also cited in Moss 2003, p. 75) aptly summarized: "At its heart, the debate centres on the extent to which the sources of order in biology lie predominantly in the stable bond structures of molecules, Schrödinger's main claim, or in the collective dynamics of a system of such molecules." That is, the debate revolves around whether genes/genomes present the 'crystalline core' of cells and organisms *versus* just 'one among many components' making up cells and organisms.

3. How the current state of knowledge in biology vindicates both life's holistic systems complexity and gene-centeredness (and falsifies both genetic determinism-reductionism and gene-de-centrism)

We will now demonstrate how the present state of knowledge in biology vindicates both life's holistically complex and gene-centred nature, while at the same time falsifies extreme genetic 'determinism' and 'reductionism' (according to which biochemical, cellular and organismal organization are quasi-exhaustively determined by and reducible to genetic sequence information) as well as extreme 'gene-de-centrism' (according to which genes are quasi-entirely 'de-centralized' and/or 'relativized' within the complex biochemical and developmental dynamics of cells and organisms).

3.1 The vindication of holistic systems complexity and the falsification of genetic determinism-reductionism

The understanding of the gene/genome as a kind of 'central source' (Griesemer 2002, 2005) or 'ROM-device' (Shapiro 2011, 2013) from which there is a quasi-unidirectional flow of order, negentropy and/or information into cellular biochemistry and development, has been challenged by data from molecular, developmental and systems biology. One of the first inroads on the orthodox 'DNA-centric' perspective prevalent during the 1950s and '60s was due to the discovery of *reverse transcription* (Crick 1970; Temin and Mizutani 1970). If reverse transcription would be non-existent or uncommon, the negentropic/informational constraints from the genome on the transcriptome would be stronger than vice versa. However, due to the high frequency rates of reverse transcription (Temin 1985; Brosius 1999, 2003; Shapiro 2009, 2011), the flow of negentropy/information among the two is far from unidirectional. In humans, for instance, over one-third of the genetic DNA-variation in the genome stems from reverse transcribed RNA (International Human Genome Sequencing Consortium 2001). Reverse transcribed RNA contributes considerably to the origin of new genetic DNA-variation in eukaryotes as well as in archaea and bacteria. Brosius (2003) has

therefore argued that it may be a relic of the evolutionary transition from the proto- or early-biotic RNA world towards the current DNA/RNA world, when RNA-genes would have been gradually replaced by and, hence, transcribed into DNA-genes. The pervasive bidirectionality of transcription among DNA and RNA seriously corrodes DNA-centrism and delivers a picture of a kind of global 'NA-genome' containing both the DNA- and RNA-sequences of the cell, as such enforcing an extension from DNA-centrism to 'NA-centrism' (De Tiège et al. 2014).

Moreover, as several critics of gene-centrism (e.g., Thieffry and Sarkar 1998; Griesemer 2002; Moss 2003; Stotz 2006a,b; Noble 2008, 2011, 2012; Shapiro 2009, 2011, 2013; Griffiths and Stotz 2013; De Tiège et al. 2014; Noble et al. 2014) pointed out, the causal flow of negentropy and information from NA-sequences all the way to cellular and organismal (phenotypic) organization, too, is far from purely unidirectional and is 'corroded', 'diluted' and 'contextualized' due to substantial *extra-genetic input*, i.e., due to *causal co-determination* by factors not reducible to the NA-sequence-specificity in the organism's genome, such as

- enzyme-, cell- and environmentally-mediated regulations of gene activity;
- enzyme-, cell- and environmentally-mediated modifications of the genome architecture (e.g., mobile genetic elements, lateral gene transfer);
- enzyme-, cell- and environmentally-mediated *pre-translational* modifications of DNA- and RNA-sequences (e.g., directed mutagenesis; changes in DNA-sequence due to proofreading and repair; DNA-methylation causing the mutation of methylated cytosine into thymine; RNA-editing; RNA-splicing);
- enzyme-, cell- and environmentally-mediated *translational* recoding such as frameshifting, programmed bypassing, and codon redefinition (Baranov et al. 2003; Stotz 2006b);
- enzyme-, cell- and environmentally-mediated *post-translational* protein modifications due to covalent alterations on the ribosomes (Shapiro 2009, 2011);
- the fact that gene products (functional RNAs and proteins) are not the sole components making up cells and organisms and the fact that genes are not the sole factors being inherited during cellular and organismal reproduction (e.g., Jablonka and Lamb 2005; Rando and Verstrepen 2007; Jablonka and Raz 2009; Lamm 2014).

These facts show how genetic sequence information is undeniably 'diluted' and 'contextualized' within the collective biochemical and developmental dynamics of cells and organisms as complex systems (cf. Callebaut et al. 2007; Noble et al. 2014). Perspectives such as genetic 'determinism' and 'reductionism' become seriously flawed if not falsified: cells and organisms are not exhaustively determined or specified by their genetic sequences – they are not reducible to the sequence information in their genomes alone. Therefore, the current state of knowledge in biology decisively falsifies genetic determinism and reductionism while at the same time vindicating life's holistic complexity.

3.2 The vindication of gene-centrism and the falsification of gene-de-centrism

Does the falsification of genetic determinism and reductionism also imply a falsification of gene-centrism? According to most critics, it does (e.g., Oyama et al. 2001; Jablonka and Lamb 2005; Stotz 2006a,b; Callebaut et al. 2007; Shapiro 2009, 2011; Noble 2008, 2010, 2011, 2012; Noble et al. 2014). They do not really distinguish gene-centrism from genetic determinism and reductionism. Gene-centrism, however, does *not* demand

(i) that every aspect of biochemical, cellular and organismal (phenotypic) organization is exhaustively determined by and reducible to genetic sequence information (i.e., genetic determinism and reductionism), *nor*
(ii) that the gene/genome is an absolutely 'sealed' central source, i.e., that there are no 'Lamarckian' violations of the Weismann barrier and the central dogma at all – thus that 'natural genetic engineering' (term Shapiro 2011, 2013) and 'downward causation' (Noble 2008, 2012) are non-existent.

Further relying on Tanghe's (2013, pp. 371-372) comparison between gene-centrism and heliocentrism, one might compare the situation with the heliocentred nature of our planetary system. Analogous to gene-centrism, heliocentrism does *not* imply

(i) that all planetary processes and behaviours are exhaustively determined by and reducible to solar processes (i.e., no 'helio-determinism' and 'helio-reductionism'), *nor*
(ii) that there are no causal influences from the planets on the sun at all.

Rather, heliocentrism refers to the fact that the sun is the (gravitational and electromagnetic) 'power centre' of the planetary system, i.e., to the fact that the causal (gravitational and electromagnetic) power or constraints from the sun on the planets are significantly *stronger* than the constraints from the latter on the former. Analogously, gene-centrism would hold if genes are at the (negentropic and informational) 'power centre' of biochemical, cellular and organismal organization, i.e., if the causal (negentropic and informational) constraints from genetic sequence-specificity on biochemical, cellular and organismal organization would be significantly *stronger* than the constraints from the latter on the former (in the 'Lamarckian', 'natural genetic engineering' and/or 'downward causation' direction). Just as the sun cannot be fully 'de-centralized' within the planetary system – the sun is not simply a heavenly body 'among' the planets – genes too could then not be fully 'de-centralized' within cells and organisms, i.e., genes would then not simply be molecules 'among' the other molecules that make up cells and organisms.

It is important to realize this, because gene-centrism is often attacked with the help of correct but inappropriate arguments, arguments that, in reality, falsify genetic determinism and reductionism but not gene-centrism in the proper sense of the word. A constantly recurring example is the (correct) statement that genes are one among many extra-genetic causal factors contributing to the biochemistry and development of cells and organisms (Oyama et al. 2001; Jablonka and Lamb 2005; Noble 2008, 2010, 2012; Noble et al. 2014).[4] Biochemistry and development are indeed not exclusively determined by and reducible to genetic information. However, although this argument works successfully against genetic determinism and reductionism, it is not an appropriate strategy to counter or falsify gene-centrism. An analogous argument, i.e., that the sun is one among many non-solar causal factors contributing to planetary processes and behaviour – thus that not everything occurring on planets is exclusively determined by and reducible to solar processes, could be used to counter or falsify 'helio-determinism' and 'helio-reductionism' but *not* heliocentrism. Indeed, the latter nevertheless holds, as the causal (gravitational and electromagnetic) constraints from the sun on the planets are significantly *stronger* than the constraints from the latter on the former, thereby allowing the sun to be the (gravitational and electromagnetic) 'power centre' of the planetary system. Hence, the key question for gene-centrism is:

[4] See also Stegmann (2012) for a philosophical analysis of the argument.

> Are genes effectively at the (negentropic and informational) 'power centre' of biochemical, cellular and organismal organization? That is, are the causal (negentropic and informational) constraints from genetic sequence-specificity on biochemical, cellular and organismal organization effectively *stronger* than the constraints from the latter on the former, thus than the constraints in the 'Lamarckian', 'natural genetic engineering' and/or 'downward causation' direction from phenotypic (cellular and organismal) organization and gene products (such as enzymes) on genetic NA-sequences?[5]

The answer is almost incontrovertibly 'yes'. The causal (negentropic and informational) constraints from genetic NA-sequences via gene products on cellular and organismal (phenotypic) organization in the 'upward', 'ontogenetic', 'Weismannian' and/or 'central dogma' direction is – in spite of all the 'corrosive' processes mentioned in section 3.1 – much more *robust, canalized and/or statistically reliable* than in the 'downward', 'Lamarckian' and/or 'natural genetic engineering' direction. If we consider the most *radical and intrusive* instances of 'Lamarckian' and/or 'downward' causation, i.e., those involving effective enzyme-, cell- and environmentally-mediated *modifications of NA-sequence-specificity* (e.g., mobile genetic elements, directed mutagenesis, changes in DNA-sequence due to proofreading and repair, DNA-methylation causing the mutation of methylated cytosine into thymine, RNA-editing and RNA-splicing), then we see that, even here, there is no such thing as a robust, canalized and/or statistically reliable 'reverse transformation' from specific functional states in gene products 'feed-backwards' into linear genetic NA-sequences, and certainly not a robust, canalized and/or statistically reliable 'reverse ontogeny' from specific functional states in cellular and organismal phenotypic organization 'feed-backwards' into linear genetic NA-sequences.

The heliocentrism analogy is particularly clarifying in this regard. Heliocentrism is based on the fact that the sun is at the (gravitational and electromagnetic) 'power centre' of the planetary system – thus on the fact that the causal (gravitational and electromagnetic) constraints from the sun on the planets are significantly stronger than the other way around. Therefore, a physical (e.g., gravitational or electromagnetic) change in the state of the sun may cause a change in the state of the planets, but a change in the state of a planet is *less likely* to cause a change in the state of the sun. And indeed, similarly, a change or mutation in genetic NA-sequence may cause a change in gene products and in phenotypic (cellular and organismal) organization, but a change in phenotypic organization or in a gene product is *less likely* to cause a change or mutation in genetic NA-sequence. That is, the negentropic-informational power from genetic sequence-specificity on gene products and phenotypic organization is indeed stronger than the power from the latter on the former. *This simple fact puts genetic sequence-specificity at the (negentropic and informational) 'power centre' of biochemical, cellular and organismal organization, in an analogous way as the sun is at the (gravitational and electromagnetic) 'power centre' of the planetary system, thus rendering invalid nearly all criticism on gene-centrism – although not on genetic determinism and reductionism – formulated during the past three decades.* While obviously causally

[5] In De Tiège et al. (2014) we demonstrated that the causal-informational constraints from genetic NA-sequences on both the conformational structure and functioning of gene products (functional RNAs and proteins) are significantly stronger and more pervasive than the other way around (i.e., than in the 'natural genetic engineering' direction), thereby justifying a modest kind of gene-centrism or 'NA-sequence-centrism' confined to the subcellular level of NA/protein-based biochemistry. However, the question on any extension or generalization of gene-centrism beyond this limited domain, i.e., to more 'peripheral' domains such as higher levels of biological organization, remained unanswered, as we did not give a reason why the (inevitably weaker) causal-informational constraints from genetic sequences on such more peripheral zones would still be stronger than those involved in the 'natural genetic engineering' of DNA- and RNA-sequences.

'integrated' and 'contextualized' within the collective biochemical and developmental dynamics of cells and organisms as complex systems, genes nevertheless *resist a full 'de-centralization' or 'relativization'* – which is in line with the position of many biologists (e.g., Gilbert et al. 1996; Hall 2001, 2003; Gilbert 2003; Haig 2007; Wagner 2014).

It is important to realize that, due to an increasing amount of intervening co-determining extra-genetic factors on the ontogenetic 'upward' causal pathway from genetic sequences via gene products all the way to biochemical, cellular and organismal organization, there is – the 'higher-up' we go – an increasing 'independency' and/or 'plasticity' of these higher levels of organization towards the genes/genome. Analogous with the planetary system: the further away from the sun, the weaker the causal (gravitational and electromagnetic) constraints from the sun on that planet or satellite. However, as long as the causal (gravitational and electromagnetic) constraints from the sun on a satellite are strong enough, the satellite is still 'captured' in the causal (gravitational and electromagnetic) 'field' of the sun. Similarly, the further away from the genes/genome, the weaker the causal (negentropic and informational) constraints from the genes/genome on that level of biological organization. However, as long as the constraints from the genes/genome on a particular level of organization are strong enough, that level would still be 'captured' in the causal (negentropic and informational) 'field' of the genes/genome. Even levels of biological organization outside the cellular boundaries of an organism, i.e., so-called 'extended phenotypic' organization (cf. Dawkins 1982, 2004), could still be 'captured' in the causal (negentropic and informational) 'field' of the organism's genes/genome. To use the planetary system analogy again, such extended phenotypes would 'circle' in a (admittedly loose) 'trajectory' around the organism's crystalline 'power centre' – its genes/genome.

3.3 Preliminary conclusion

The preceding considerations can be summarized as follows: the present state of knowledge in biology strongly suggests that life on Earth should be regarded both (i) holistically and dynamically complex and (ii) gene-centred. (i) Holism/complexity refers to the causal 'integratedness' or 'contextualizedness', and *not* to a radical 'de-centeredness', of genes within the complex biochemical and developmental dynamics of cells and organisms. And (ii) gene-centrism refers to the causal (negentropic and informational) constraints from genetic sequence-specificity on biochemical, cellular and organismal organization being significantly stronger than the other way around, and *not* to a radical genetic 'determinism' and 'reductionism' according to which biochemical, cellular and organismal organization are quasi-exhaustively determined by and reducible to genetic information. The extreme and radical perspectives are falsified while the moderate perspectives are vindicated by the current state of knowledge of life on Earth.

3.4 The vindication of both life's holistic systems complexity and gene-centeredness (and the falsification of both genetic determinism-reductionism and gene-de-centrism) by cross-species genome transplantations

In this final subsection, we want to indicate that the results of bacterial genome transplantation and cross-species cloning, in one time, empirically vindicate both life's holistic systems complexity and gene-centeredness while falsifying both radical genetic determinism-reductionism and gene-de-centrism.[6] In 2007, the J. Craig Venter Institute transplanted the genome of one bacterial species (*Mycoplasma mycoides*) into another, closely related (genome-deprived) bacterial species (*Mycoplasma capricolum*), thereby turning the recipient species into the donor species (Lartigue et al. 2007). As Pennisi (2007) remarked,

[6] Some of the reasoning in this section can already be found in Tanghe (2013, pp 386-389).

the experiment has only been carried out between two closely related microbial species lacking cell walls. Indeed, donor genetic sequences cannot do anything without recipient biochemical and cellular organization, not even without recipient organization that is closely related and somehow 'compatible' with the donor genetic material, thereby unambiguously displaying life's holistically complex nature. But contrary to what one might think at first sight, this does not undermine gene-centrism. Relevant for gene-centrism is the question whether the negentropic-informational (transformational) constraints from (donor) genetic sequences on (recipient) biochemical and cellular organization are *stronger* than those from the latter on the former (cf. section 3.2). This is undeniably the case here: the donor genes transform the recipient cell into a donor species cell, whereas the recipient biochemical and cellular organization does *not* transform the donor genes into recipient species genes. More precisely, when we *balance* the negentropic-informational (transformational) power of (donor) genetic sequences *versus* (recipient) biochemical and cellular organization, then – after fusing both powers – there are three theoretical possibilities:

- The resulting species is more like the recipient species (which is not the case): the negentropic-informational constraints of the (recipient) biochemical and cellular dynamics would be stronger than those of the (donor) genetic sequences.
- The resulting species is a hybrid (which is also not the case): the negentropic-informational constraints of the (recipient) biochemical and cellular dynamics and the (donor) genetic sequences would be about equally strong.
- The resulting species is more like the donor species (which it is): the negentropic-informational constraints of the (donor) genetic sequences are stronger than those of the (recipient) biochemical and cellular dynamics.

That is, the negentropic-informational constraints imposed by (donor) genetic sequence-specificity on (recipient) biochemical and cellular organization appear to be definitively *stronger* than the constraints from the latter on the former, resulting in a bacterial cell that definitively belongs to the donor genetic species, thus displaying genes at the 'power centre' of (microbial) life.

A similar rationale applies to *cross-species cloning* experiments in eukaryotes: the nuclear genome of one (endangered or even extinct) species is inserted into the enucleated egg cell of a related (more common) species, thereby converting the recipient species into the donor species (e.g., Lanza et al. 2000; Loi et al. 2001, 2007; Gomez et al. 2004; Williams et al. 2006; Folch et al. 2009; Hajian et al. 2011). Life's holistically complex nature is apparent from the indispensable role of the biochemical and cellular organization of the recipient egg cell, among others, in the process of 'nuclear reprogramming', which refers to the structural and functional chromatin modifications that are imposed by the enucleated host oocyte on the inserted nuclear genome to restore the totipotency of the zygotic nucleus. Until now, in only a minority of cross-species cloning experiments the totipotency of the zygotic nucleus is successfully restored; in the majority of cross-species clones epigenetic drift leads to abnormal, non-viable epiphenotypes, explaining the large number of early deaths both before and after birth. These difficulties notwithstanding, in all of the cases the (non-viable and viable) embryos and born individuals definitively belong to the nuclear donor species and not to the enucleated host egg cell species (neither are they hybrids) (cf. Tanghe 2013, pp 386-389). It is therefore beyond any doubt that, as in the bacterial genome transplantation experiment, the negentropic-informational (transformational) constraints from (donor) genetic sequence-specificity on (recipient) biochemical and cellular organization are definitively *stronger* than the constraints from the latter on the former, thereby putting genes at the 'power centre' and displaying life's gene-centred aspect.

Although in *cross-genus* cloning the causal constraints from (recipient) cytoplasmic egg cell factors on (donor) gene regulation and expression are somewhat more striking (Sun and Zhu 2014), there is no mention of substantial modifications of (donor) genetic *sequence-specificity*. Therefore, here too, the negentropic-informational (transformational) constraints from (donor) genetic sequence-specificity on (recipient) biochemical and cellular organization appear to be definitively *stronger* than the constraints from the latter on the former, thus displaying life's gene-centeredness. For example, although the implementation of the nuclear genome of a common carp (*Cyprinus carpio*) into the enucleated egg cell of a goldfish (*Carassius auratus*) resulted in offspring with a goldfish number of vertebrae (due to gene regulation mediated by recipient cytoplasmic egg cell factors), the offspring definitively belongs to the nuclear donor carp species. As Sun et al. (2005, p. 513) report, "the morphological data are solid evidence that the common carp nuclei directed the development of the cross-genus cloned fish."

The indispensability of extra-genetic such as epigenetic, cytoplasmic and ecological elements of the recipient egg cell species (Noble 2008, 2011) does not falsify the gene-centred aspect of life (cf. Tanghe 2013, pp 386-389). Surely, donor genetic sequences cannot do anything without recipient extra-genetic organization, not even without recipient organization that is relatively closely related to and compatible with the donor genetic material, thus displaying life's holistically complex nature. However, this does not undermine life's gene-centeredness, since the latter relies on the negentropic-informational (transformational) constraints from (donor) genetic sequence-specificity on (recipient) biochemical and cellular organization being significantly *stronger* than the constraints from the latter on the former, which is also displayed in these experiments. Therefore, the data on bacterial genome transplantation and cross-species/genus cloning unequivocally (i) support or vindicate *both* life's holistic complexity and gene-centeredness and (ii) disprove or falsify *both* extreme or radical genetic determinism-reductionism and gene-de-centrism.

4. From the proximate to the evolutionary level: some implications for evolutionary theory

Without entering into extensive details about the theoretical and bio-philosophical discussions that take place within modern evolutionary theory, we will nevertheless point to some important implications for the controversy between the Modern Synthesis and a so-called 'Extended Synthesis' (e.g., Pigliucci and Müller 2010; Noble et al. 2014; Laland et al. 2014). The Modern Synthesis originally grew out of the synthesis between Mendelian genetics and Darwinian evolutionism (Huxley 1942; Mayr and Provine 1980). From the beginning, the focus was on the role of genes in evolution: gene and genotype selection, genetic drift, genetic mutation, genetic recombination, and gene flow. Advocates of an Extended Synthesis plead for the incorporation of extra-genetic higher-level causation in evolution. Some important, partially overlapping examples are directed mutagenesis (Jablonka and Lamb 2005, chapter 3; Rando and Verstrepen 2007) and natural genetic engineering (Shapiro 2011, 2013), epigenetic causation and inheritance (Rando and Verstrepen 2007; Jablonka and Raz 2009), developmental, phenotypic and behavioural plasticity and inheritance (West-Eberhard 2003; Moczek et al. 2011), niche construction and inheritance (Scott-Phillips et al. 2014), and multilevel selection processes (Okaska 2006; Godfrey-Smith 2009).

The empirical data on extra-genetic causation in evolution are solid, although relatively scarce compared to the overwhelming data on genetic causation (gene and genotype selection, genetic drift, genetic mutation, genetic recombination, and gene flow). On the one hand, as already underscored, gene products and phenotypic (cellular and organismal)

organization are not exhaustively determined by and reducible to genetic sequence-specificity (i.e., no genetic determinism and reductionism). This not-to-genes-reducible complexity and specificity causally (biochemically, physiologically, developmentally, behaviourally) interacts with the environment, and is thus expected to play an equally not-to-genes-reducible causal role in evolutionary processes. As such, life's holistically complex aspect would naturally extend from the proximate to the evolutionary level. That is, biological evolution would not be exhaustively reducible to genetic evolution and, for example, evolution by natural selection would not be exhaustively reducible to gene and genotype selection (cf. Okaska 2006; Godfrey-Smith 2009).

On the other hand, since the causal (negentropic-informational) constraints from genetic sequence-specificity on gene products and phenotypic (cellular and organismal) organization are significantly *stronger* than those from the latter on the former (see supra), extra-genetic higher-level processes – which are virtually *permeated* by functional gene products (functional RNAs and proteins) and, hence, by genetic sequence-specificity – could never be fully divorced from their genetic base or 'centre'. As Wray et al. (in Laland et al. 2014, p. 164), for instance, write on epigenetic causation in evolution: "we know of no case in which a new trait has been shown to have a strictly epigenetic base divorced from gene sequence." Although epigenetic specificity is not exhaustively determined by and reducible to genetic sequence-specificity (i.e., no genetic determinism and reductionism), the negentropic-informational constraints from genetic sequence-specificity on epigenetic specificity are significantly *stronger* than the constraints from epigenetic causation (through 'natural genetic engineering' – see section 3.1) on genetic sequence-specificity. That is, the flow of statistical negentropy and information from the genetic sequence level to the epigenetic level is significantly *stronger* than in the opposite direction. More generally, since genes resist a full 'de-centralization' in the biochemistry and development of cells and organisms (see supra), genes could also not be fully 'de-centralized' in the causal (biochemical, physiological, developmental, behavioural) interaction processes of cells and organisms with their environments and, thus, in the evolutionary process. Hence, life's gene-centred aspect, too, would naturally extend from the proximate to the evolutionary level.

Thus while the Modern Synthesis was arguably too narrowly focussed on genetic causation, the latter cannot simply be de-centralized either. Therefore, the term 'Postmodern Synthesis' (Whitfield 2008) seems inappropriate. But an 'Extended Synthesis' that takes into account irreducible extra-genetic causation in evolution (Pigliucci and Müller 2010; Laland et al. 2014), as well as an 'Evolutionary Systems Biology' that takes into account the different levels of network complexity in which life is organized (Medina 2005; Koonin and Wolf 2006; Soyer 2012), seem preferable, however, without losing sight or touch with the genetic or 'crystalline' centre or baseline around or upon which all those levels are organized. Indeed, biological evolution should be viewed as *both* a holistically complex and gene-centred process; *both* aspects of life's nature most likely extend from the proximate to the evolutionary level.

5. Conclusion and further prospects

Both intra-molecular crystalline genetic sequence-specificity and inter- and supra-molecular holistic network complexity are constitutive properties of life on Earth. On the one hand, life is holistically and dynamically complex: it is constituted by complex *inter- and supra-molecular* network dynamics and interconnectivity. On the other hand, this inter- and supra-molecular network organization is virtually *permeated and constrained* by functional gene products (i.e., functional RNAs and proteins) and, hence, by genetic sequence information

derived from the *intra-molecular crystalline* structure of nucleic acid sequences. Recognizing only one of life's characteristics, whether this be holistic network complexity or gene-centeredness, prevents a more balanced and complete understanding of life's multifaceted nature. Due to the ground-breaking advances in molecular biology and genetics during the second half of the twentieth century, intensive focus was laid on life's gene-centred aspect while holistic network dynamics was under-investigated or even neglected. At present, however, due to current successes in systems biology, some authors underestimate – or are even unwilling to recognize – life's gene-centred aspect. As such, they 'over-jump' or 'cover up' the very 'subtle' and 'fine-grained' intra-molecular crystalline aspect of life.

Here, we showed that the main argument raised against gene-centrism, viz., that genes are one among many extra-genetic causal factors contributing to the biochemistry and development of cells and organisms (e.g., Oyama et al. 2001; Jablonka and Lamb 2005; Noble 2008, 2010, 2012; Noble et al. 2014), only undermines or falsifies genetic determinism and reductionism but not gene-centrism. More broadly, we showed how the current state of knowledge in biology strongly suggests that life on Earth should be regarded as both (i) holistically and dynamically complex and (ii) gene-centred. (i) Holism/complexity refers to the causal 'integratedness' or 'contextualizedness', and *not* to a radical 'de-centeredness', of genes within the complex biochemical and developmental dynamics of cells and organisms. And (ii) gene-centrism refers to the causal (negentropic and informational) constraints from genetic sequence-specificity on biochemical, cellular and organismal organization being significantly stronger than the other way around, and *not* to a radical genetic 'determinism' and 'reductionism' according to which biochemical, cellular and organismal organization are quasi-exhaustively determined by and reducible to genetic information. We also underscored how bacterial genome transplantation and cross-species cloning experiments, in one time, empirically falsify the extreme or radical perspectives while vindicating the moderate perspectives. Finally, we indicated that life's dual nature most likely extends from the proximate to the evolutionary level, a conclusion that bears some relevance to the controversy between the Modern Synthesis and an 'Extended Synthesis'.

Concerning future prospects, much work remains to be done, especially on the conceptual integration between twentieth-century gene-centred disciplines (e.g., population and evolutionary genetics, molecular biology and genetics) and other, more recent branches such as systems biology and evolutionary developmental biology (cf. De Backer et al. 2010; Pigliucci and Müller 2010; Noble et al. 2014). Of crucial importance in this endeavour is not to undermine or neglect one of life's constitutive aspects. It is obvious that a strategy that tries to 'reduce' all inter- and supra-molecular dynamics and extra-genetic complexity to genetic variation is not an option. However, neither is a strategy that tries to radically 'de-centre' or 'relativize' genetic sequence-specificity within the overall dynamics of cells and organisms. A more subtle approach is required: integration/contextualization *through* centralization, or centralization *through* integration/contextualization.

Acknowledgements: Preparation of this manuscript was made possible by the Fund for Scientific Research Flanders (FWO), Belgium (Project number: G001013N).

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