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The modern versus extended evolutionary synthesis – Sketch of an intra-genomic gene's eye view for the evolutionary-genetic underpinning of epigenetic and developmental evolution

Alexis De Tiège[1]*, Stefaan Blancke[2] and Johan Braeckman[1]

[1]Department of Philosophy and Moral Sciences, Ghent University, Blandijnberg 2,9000 Ghent, Belgium
[2]Department of Philosophy, Tilburg University, Warandelaan 2, 5037 AB Tilburg, The Netherlands

Corresponding author
Alexis De Tiège
Department of Philosophy and Moral Sciences
Ghent University
Blandijnberg 2
9000 Ghent, Belgium
Tel. 0032(0)497859638
E-mail: alexis.detiege@ugent.be

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ABSTRACT

Studying the phenotypic evolution of organisms in terms of populations of genes and genotypes, the Modern Synthesis (MS) conceptualizes biological evolution in terms of 'inter-organismal' interactions among genes sitting in the different individual organisms that constitute a population. It 'black-boxes' the complex 'intra-organismic' molecular and developmental epigenetics mediating between genotypes and phenotypes. To conceptually integrate epigenetics and evo-devo into evolutionary theory, advocates of an Extended Evolutionary Synthesis (EES) argue that the MS's reductive gene-centrism should be abandoned in favor of a more inclusive organism-centered approach. To push the debate to a new level of understanding, we introduce the evolutionary biology of 'intra-genomic conflict' (IGC) to the controversy. This strategy is based on a twofold rationale. First, the field of IGC is both 'gene-centered' and 'intra-organismic' and, as such, could build a bridge between the gene-centered MS and the intra-organismic fields of epigenetics and evo-devo. And second, it is increasingly revealed that IGC plays a significant causal role in epigenetic and developmental evolution and even in speciation. Hence, to deal with the 'discrepancy' between the 'gene-centered' MS and the 'intra-organismic' fields of epigenetics and evo-devo, we sketch a conceptual solution in terms of 'intra-genomic conflict and compromise' – an 'intra-genomic gene's eye view' that thinks in terms of intra-genomic 'evolutionarily stable strategies' (ESSs) among numerous and various DNA regions and elements – to evolutionary-genetically underwrite both epigenetic and developmental evolution, as such questioning the 'gene-de-centered' stance put forward by EES-advocates.

KEYWORDS: epigenetics, evo-devo, gene's eye view, selfish gene(tic element), intra-genomic conflict and compromise, evolutionarily stable strategy (ESS).

INTRODUCTORY BACKGROUND: OUTLINE OF THE PROBLEM AND OBJECTIVES

From their inception in the 1920s and 1930s, the Modern Synthesis (MS) and its formal-mathematical foundation of population genetics have aimed at providing a unifying theoretical framework for evolutionary-biological research.[1,2] Four 'gene-centered' forces that direct evolution are distinguished: mutation, drift, selection and gene flow. Interpreting and modelling the phenotypic evolution of organisms in terms of 'changes in gene frequencies' relies on the abstract assumption of a *statistically reliable correlation between genotype and phenotype*. From the 1980s on, however, newly emerging fields like molecular epigenetics and evolutionary developmental biology (evo-devo) started to explore the previously abstracted or 'black-boxed' epigenetic and developmental processes that mediate between the genotypic and phenotypic level.[3,4] For some decades now, several philosophers of biology and philosophically inclined biologists[5-12] have been claiming that the gene-centered MS lacks the conceptual and explanatory potential to assimilate the newly revealed 'extra-genetic' epigenetic and developmental complexity. During the last ten

years they have developed the so-called 'Extended Evolutionary Synthesis' (EES) which rests, among others, on the following two claims:

(1) extra-genetic – epigenetic and developmental – complexity, specificity or information is underdetermined by, or irreducible to, the underlying genetic information residing in the genome;
(2) this extra-genetic epigenetic and developmental information has a causal-directional effect on evolution.

In other words, the MS's gene-centrism is questioned, and it is opted for a *more inclusive organism-centered* perspective on biological evolution characterized by a *gene-de-centered and/or distributed complexity*.[5-12] By contrast, defenders of the gene-centered MS argue that the evolution of epigenetic and developmental complexities can be ultimately accounted for by the underlying population genetics and, hence, that the alleged causal-directional role of epigenetic and developmental processes in the course of evolution is yet ultimately a genetically steered influence on evolution.[13-16] Both epigenetic variability and developmental plasticity/accommodability, for example, would be genetic(ally underwritten) adaptations or 'cranes'[17] that evolved by natural gene selection under – and thus to cope with – varying environmental conditions.[14,15,18] That is, both epigenetics and development could be integrated into the existing gene-centered MS without much conceptual adjustment, let alone requiring fundamental or 'revolutionary' change.[13-22]

What plagues the whole controversy, however, is that there seems to be, at present, no general evolutionary-theoretic and evolutionary-genetic framework or model on epigenetics and development.[23,24] The underlying reason for this lacuna is a *significant difference in approach and perspective between the MS and population genetics versus epigenetics and evo-devo*. The first two are characterized by 'population thinking', i.e., they think in terms of populations of genetically represented organisms, as such conceptualizing biological evolution in terms of 'inter-organismal' interactions among genes sitting in different individual organisms that constitute a population. The latter two, by contrast, consider individually developing organisms, i.e., the 'intra-organismal' molecular epigenetics and physiological development of individual organisms.[9,23,24] The issue at stake is thus:

> How can 'intra-organismal' epigenetics and development be conceptually integrated into population-based evolutionary theory and genetics?

To address this problem, we introduce the evolutionary biology of 'intra-genomic conflict' (IGC) and a broader 'intra-genomic gene's eye view' to the MS/EES debate. As this field is gene-centered (cf. the MS) *as well as* intra-organismic (cf. the fields of epigenetics and evo-devo that the EES aims to integrate into evolutionary theory), it could provide for a conceptual and explanatory bridge or common ground between the abovementioned two seemingly incompatible approaches or paradigms. This 'duality' that characterizes the biology of IGC requires some more explanation.

First, concerning its conceptual link to the gene-centered MS, the evolutionary biology of IGC has its historical roots in this framework and, more specifically, in the MS's more recently developed variant – the 'gene's eye view' or 'selfish gene' theory of evolution.[13-15,25-36] Here, evolution is conceptualized in terms of interactions, competition and cooperation among single genes, usually 'inter-organismal' ('inter-allelic') competition and cooperation among genes (alleles) sitting in different (competing and cooperating) organisms, but also and most importantly 'intra-organismic' and 'intra-genomic' conflict/competition and compromise/cooperation among genes sitting within the same organism and genome. As Dawkins wrote:

> "[…] interactions between genes sitting in different bodies are only the tip of the iceberg. The vast majority of significant interactions between genes in the evolutionarily stable set – the gene pool – go on within individual bodies. […] Well-integrated bodies exist because they are the product of an evolutionarily stable set of selfish genes."[28]

> "In a sense, the whole process of embryonic development can be looked upon as a cooperative venture, jointly run by thousands of genes together. […] In natural selection, genes are always selected for their capacity to flourish in the environment in which they find themselves. We often think of this environment as the outside world, the world of predators and climate. But from each gene's point of view, perhaps the most important part of its environment *is all the other genes that it encounters*. And where does a gene 'encounter' other genes? Mostly in the cells of the successive individual bodies in which it finds itself. Each gene is selected for its capacity to cooperate successfully with the population of other genes that it is likely to meet in bodies."[37]

This 'intra-organismic gene's eye view', i.e., this *shift of perspective from competition among different alleles towards competition among genes within the same system, genome or organism*, was instrumental in the rise of the evolutionary biology of IGC and selfish genetic elements, i.e., elements of which the fitness interests are in conflict with other elements in the genome and with the genome as a whole. Early publications on this subject[38,39] also explicitly referred to Dawkins.[28]

Second, concerning its conceptual link to 'intra-organismal' epigenetics and evo-devo, there is a rapidly growing body of empirical evidence of the causal-directional role and significance of IGC in epigenetic gene regulation, developmental evolution and even speciation.[40-48] The absence of any reference to, let alone discussion of, this body of literature and IGC in general presents *a serious gap or hiatus* in the EES-literature.

However, the evolutionary biology of IGC and a more general 'intra-genomic gene's eye view' would not just be in continuation to the MS. According to the classical *status quo* of the

MS, (genotypically represented) organisms are 'units of fitness' whose adaptive design is produced through evolution by natural selection. All genes share a common fitness interest, and cases of IGC (i.e., fitness differences among genes within the same genome/organism) are discarded as ignorable exceptions to the rule.[49] However, the rapidly increasing evidence of the *non-negligible* causal role of IGC in organismal evolution and speciation forces to re-define the 'organism' as an evolutionarily stable adaptive 'compromise' among basically or fundamentally selfish or conflicting genetic interests.[34,36,40] That is, the evolution of whole genomes and organisms would require a re-conceptualization and refinement in terms of an 'intra-genomic gene's eye view' with the single 'genetic element' as the 'unit of fitness'. This would imply a 'molecular gene's eye view' according to which the genome is a 'molecular ecosystem'[34,42,50] constituted by populations of genetic elements that are shuffled and recombined during evolution and are characterized by different kinds of interactions ranging from competition and conflict to compromise and cooperation. Such thinking in terms of evolutionary interactions among genes within the genome, e.g., among structural and regulatory sequences, could allow to consider a *combinatorial increase of genetic sequence information.*[36] The question remains, however, to what extent this increased genetic information – this 'non-reductive gene-centrism' – would suffice to generate and support the allegedly irreducible complexity of epigenetic and developmental processes. In the present paper we propose and explore the conceptual and explanatory potential of an intra-genomic 'molecular ecosystem' framework to serve as underlying evolutionary theory and genetics within which the intra-organismal fields of epigenetic and developmental evolution can be conceptually grounded. That is, we propose an 'intra-genomic gene's eye view' to evolutionary-theoretically and -genetically underpin intra-organismal epigenetic and developmental evolution.

This proposal would also *challenge current 'gene-de-centric' EES-thinking*. Current EES-proposals are rather encompassing in their addition of 'extra-genetic' fundamental terms and explanatory tools to the existing MS framework and, for this reason, have difficulty to find entrance into the scientific community of evolutionary biologists.[15,16,18-21] By contrast, the evolutionary biology of IGC and a more general 'intra-genomic gene's eye view' may offer a more *economical or parsimonious* alternative, keeping its fundamental concepts and explanatory tools in terms of genes and genetics. As such, the existing gene-centered framework of the MS could be largely maintained without the need to call in additional, more inclusive/extended causal factors at the fundamental explanatory level. This would not be the first time that the gene-centered MS could eventually be adjusted to novel, seemingly extra-genetic or gene-de-centered research findings, without being forced to undergo a 'revolutionary' paradigm shift by giving up its gene-centered explanatory foundation.[51]

We will use the above-proposed 'intra-genomic conflict/compromise' or 'molecular ecosystem' approach according to which the genome is a set or population of 'genetic elements' that are shuffled and recombined during evolution and are characterized by different kinds of behavioral-ecological and game-theoretical interactions ranging from competition and conflict to compromise and cooperation. Darwinian 'units' or 'individuals',[52] here genes, although basically in competition and conflict with each other, are predicted to eventually 'co-adapt' – through constant interaction – to each other's presence, as such giving rise to 'evolutionarily stable compromises', which can be game-theoretically formalized through the concept of the 'evolutionarily stable strategy' or 'ESS'.[53] We propose the game-theoretical ESS-approach to the intra-genomic level[54] as a means or method to *evolutionary-genetically underpin* 'intra-organismal' epigenetic and developmental evolution.

In what follows, we present a sketch of an intra-genomic ESS-modelling of epigenetic and developmental evolution. We depart from the oft-made distinction between two levels of epigenetics.[55-57]

- a lower-level 'molecular epigenetics'[58] as the study of molecular mechanisms for gene expression and regulation and, as such, a subfield of contemporary molecular biology. When such gene/genome expression patterns are mitotically and/or meiotically inherited without underlying changes in genetic DNA sequences, this is called 'epigenetic inheritance'.[59]
- a higher-level 'developmental epigenetics'[60] referring to the study of cellular, physiological and morphological developmental processes and, as such, part of present-day evo-devo. Here too, developmental patterns can be transgenerationally inherited through causal pathways other than underlying gene sequences.

We propose an intra-genomic ESS-approach for the evolutionary-genetic underpinning of:

- molecular epigenetics incl. epigenetic inheritance;
- the developmental epigenetics of higher-level organization, modularity and homology;
- the developmental epigenetics of phenotypic plasticity, evolvability and evolutionary change.

SKETCH OF AN INTRA-GENOMIC ESS-APPROACH TO EPIGENETIC AND DEVELOPMENTAL EVOLUTION

An intra-genomic ESS-approach to the evolutionary-genetic underpinning of molecular epigenetics: During the molecular information flow from genetic DNA-sequences to either final noncoding RNA (ncRNA) product or – via mRNA and amino acid sequence – final protein product, several processes of sequence modification, preparation, editing or engineering occur. Some theorists that are opposed against the gene-centered MS therefore argue that these final gene products (proteins and, to a lesser extent, ncRNAs) are not exclusively determined or encoded by genetic DNA-sequences, but are 'engineered' or 'constructed' through molecular regulatory mechanisms and processes they term 'natural genetic engineering'[61,62] and 'mo-

lecular epigenesis'[63,64] to explicitly relativize or de-centralize the determining role of genes in it. Examples of such processes co-influencing or co-determining the structure of final gene products are:[61,62,64]

- pre-transcriptional modifications of DNA-sequence (e.g.,reverse transcription, changes in DNA-sequence due to proofreading and repair, DNA-methylation causing the mutation of methylated cytosine into thymine);
- post-transcriptional modifications of RNA-sequence (e.g., RNA-editing, RNA-splicing);
- translational recoding (e.g., frameshifting, programmed by-passing, codon redefinition);
- post-translational protein modifications due to covalent alterations on the ribosomes.

And examples of – often 'epigenetically inheritable' – molecular-epigenetic processes involved in gene regulation are: chromatin-marking like DNA-methylation, sRNA-mediated epigenetic regulation and inheritance, structural 3D inheritance like prions, and self-sustaining metabolic loops.[59] Given the increasingly revealed efficacy of such processes and mechanisms, many theorists have concluded that the transcriptome, the proteome and the epigenome would all be *underdetermined* by the genome and that molecular epigenetics cannot be reduced to the underlying genetics.[56,59,61-64]

To elucidate this problem, we use the abovementioned intra-genomic conflict/compromise framework to model the genome as a 'molecular ecosystem' consisting of several types of interacting (coding, non-coding, *cis*-regulatory, etc.) DNA elements or regions. This permits us to conceptualize and model the molecular epigenesis of gene products and regulatory patterns (incl. the latter's 'epigenetic inheritance') as *an evolved and evolutionarily stable – thus ESS-based – cooperative enterprise among different types of interacting DNA regions or elements within the genome*. Such a modelling would also allow to consider a *combinatorial increase of genetic information*. It is indeed true that the transcriptome, proteome and epigenome are informationally underdetermined by the genome when the latter is conceived simply as a reservoir of gene sequences. Jablonka and Raz,[59] for example, have convincingly demonstrated that epigenetic specificity and variation do not always co-vary with – and are informationally underdetermined by – underlying genetic DNA sequence-specificity. However, this would not necessarily be the case when the genome is approached from an intra-genomic perspective incorporating all the *combinatorial* interactions among, and concomitant increase of, genetic information. As such, the 'epigenesis' of gene products and regulation patterns – incl. the latter's 'epigenetic inheritance' – could be *evolutionary-genetically substantiated*, and the genome could be conceived as a truly epigenetic system containing enough combinatorial information potential to underwrite the transcriptome, proteome and epigenome. That is, in opposition to the claims made by Jablonka and other 'gene-de-centric' EES-advocates, epigenetic variants – incl. the 'epigenetically inheritable' ones – would then be ultimately 'genetically encoded'. They would be underwritten by 'intra-genomic strategies among genes', i.e., by intra-genomic ESS-based compromises among numerous ultimately selfish genetic (coding, non-coding, *cis*-regulatory, etc.) DNA regions and elements. Moreover, due to the *transgenerational persistence or inheritance potential* of intra-genomic ESSs underwriting (heritable) epigenetic states, there would be no need to call in the concept of extra-genetic 'epigenetic inheritance' as a separate inheritance system independent from genetics[59]: as epigenetic variation would ultimately rest on intra-genomic combinatorial ESS-based variation, so-called 'heritable epigenetic variation' would *de facto* be 'heritable genotypic variation'.

This proposal challenges – and is arguably resistant against – important bio-philosophical criticism on the gene-selectionist or gene's eye view. Many DNA regions and elements (both coding and noncoding) are extremely ancient and are used and recombined throughout evolution to serve as resources or building blocks for many functional products and patterns and, hence, for many adaptive organismal features. Therefore, they would transcend and lack any determinable relationship to *specific* adaptive functionality.[64,65] *Ergo*, the gene-selectionist or gene's eye view would be irrelevant. However, a specifically *intra-genomic* perspective could provide a solution to this problem. From the classical 'extra-organismal' adaptationist perspective, there are *local and temporal* environmental selection pressures for the production of specific functional molecular gene products involved in the generation of specific phenotypic adaptive features. By contrast, the 'intra-genomic' selective environment to which each genetic element is forced to adapt consists of the other elements in the genome: throughout evolution there is a *quasi-constant selection pressure for intra-genomic mutual co-adaptation*, i.e., for 'co-operability', 're-combinability' and biochemical 'versatility' to synthesize an indefinite range of molecular gene products. Hence, non-classical or intra-genomic selection pressures and adaptation may *transcend* local and temporal classical or extra-organismal selection pressures and adaptation.[36] Therefore, unlike the claims made by its critics, the gene-selectionist or gene's eye view may remain very relevant and clarifying and, moreover, applicable to the above-discussed issue on molecular epigenetics. More specifically, in order to evolutionary-genetically underpin the field of molecular epigenetics, i.e., in order to conceptually integrate molecular epigenetics into evolutionary genetics, the 'molecular epigenesis' of gene products and regulatory patterns incl. the latter's epigenetic inheritance could be re-conceptualized and re-modelled in terms of *intra-genomic ESS-based co-adaptations, compromises and cooperation* among basically selfish/competing/conflicting DNA regions and elements – the elementary building blocks of the genome.

An intra-genomic ESS-approach to the evolutionary-genetic underpinning of the developmental epigenetics of higher-level organization, modularity and homology: Organisms are structurally and functionally organized into 'individuated' or 'modular' subunits, such as the molecular structures and metabolic pathways in prokaryotes (bacteria, archaea), the organelles in eukaryotes, and the cell types, tissues, organs and anatomical parts in multicellular organisms.[4,66,67] Research in developmen-

tal genetics and evo-devo revealed that such individuated modules are genetically underwritten by gene regulatory networks (GRNs) – genomic subunits consisting of functionally organized coalitions of genes. Apart from their species-specific structural and functional variation or 'character states', these modular *baupläne* are also characterized by cross-species homology or 'character identity' underwritten by very ancient regulatory (e.g., homeobox) genes and networks,[68] termed 'character identity networks' (ChINs) by Wagner.[69,70] Many theorists and philosophers of biology claim that the developmental epigenetics of modularity and homology exceeds or transcends both (i) gene-centrism and (ii) adaptationism, two explanatory pillars of the MS.[66,71,72] Again, we propose that an intra-genomic ESS-approach (see supra) can be used as a methodological tool to not only challenge this view but also provide a solution to the twofold problem:

(i) **Gene-centrism:** As in the previous section on molecular epigenetics, to tackle and counter the alleged shortage of genetic information in the genome to code for allegedly 'irreducible' developmental-epigenetic complexity, GRNs (incl. homologous ChINs) should be re-conceptualized and re-defined in terms of *intra-genomic ESS-based compromises* among numerous genetic elements, as such demonstrating a *combinatorial increase of genetic information*. To underwrite the latter even more, the more recent branch of *nonlinear multiplayer* evolutionary game theory could be called in, which has the advantage that "[…] multiplayer games can be introduced in all the fields where evolutionary game theory is already well established. However, the inclusion of non-linearities can help to advance the analysis of systems which are known to be complex".[73,74]

(ii) **Adaptationism:** Homologous modularity and its underlying ChINs by far transcend specific (local and temporal) adaptive functionality and, as such, seem to defy an adaptationist conceptualization. They appear to have an inherent non-adaptive *robustness* that protects or *buffers* them against the degenerating effects of random mutation and drift. This robustness turns out to be so strong that it even puts structural *constraints* upon further adaptive evolution[71,75] and *canalizes* the flow of new variation to selection, as such shaping new evolutionary trajectories.[70,72,76] Crucial again (as in the previous section) is the *shift of perspective from classical 'extra-organismal' adaptation towards 'intra-genomic' adaptation*: the intra-genomic selective environment in which genetic elements co-adapt to each other's presence and form ESS-based compromises is much more stable and reliable on the long term than the external environment and, as such, transcends the relatively local and temporal adaptive pressures imposed by the outside environment on the organism. Therefore, an intra-genomic 'molecular ecosystem' perspective predicts that during evolution regulatory and other ancient elements would become *deeply co-adapted, compromised, interdependent* and hence *not easily removable* and thus *buffered against arbitrary (evolutionary) change*. This intuitive insight can be further substantiated with the game-theoretical logic of an ESS. The latter is by definition a strategy that under the prevailing environmental (here: intra-genomic) conditions cannot be bettered by an alternative strategy:[53] it is resistant or *dynamically buffered or robust* against 'invaders' (e.g., against 'degenerating' invading variation due to genetic mutation and drift) when played by a large enough number of individuals. As such, the dynamical buffering and robustness of homologous modularity would follow from the adaptationist game-theoretic logic of multiplayer ESSs itself. That is, we suggest that such an *intra-genomic ESS-approach* has the potential to evolutionary-genetically underwrite and predict phenomena of developmental modularity and homology, i.e., developmental 'robustness' and 'buffering' against unbounded pleiotropy and arbitrary new variation and evolutionary change.[70]

An intra-genomic ESS-approach to the evolutionary-genetic underpinning of the developmental epigenetics of phenotypic plasticity, evolvability and evolutionary change: Here, the *explanandum* is not cross-species homologous modularity robustly buffered against arbitrary evolutionary change, but species-specific plasticity, evolvability and evolutionary change, i.e., the potential of epigenetic developmental systems to plastically and often adaptively vary and accommodate to changes or fluctuations in the environment. The *explanans* offered by critics of the gene-centered MS in favor of a more inclusive organism-centered evolutionary theory[10,11,76,77] is that such developmental accommodations are initially non-genetic by nature and may also be non-genetically transmitted to the offspring. Only afterwards, they would become genetically hardwired or stabilized through 'genetic assimilation' and/or 'accommodation'. That is, instead of steering evolution, genes would be rather 'followers' in evolution, functionally integrated and de-centralized within more inclusive epigenetic developmental processes, the true causal determinants or drivers of evolution. Again, we propose to challenge and provide an explanatorily more parsimonious alternative to this view by means of a gene-centered game-theoretic methodology in terms of *intra-genomic* ESS-based conflict and compromise:

- First of all, multiplayer ESS-based populations can – in response to changing environmental or boundary conditions – discretely or robustly change or 'flip' from one ESS-state towards an alternative one. Applied to the intra-genomic level, the model would predict discrete adaptive accommodations of ESS-based GRNs in response to changed environmental conditions, as such providing for an evolutionary-genetic underpinning of the concept of 'genetic accommodation' underwriting a developmental accommodation. The model would thus challenge, and offer a more parsimonious alternative to, the 'genes-as-followers' thesis, as this latter is forced to call in extra-genetic and higher-level developmental causation/dynamics/accommodation/inheritance *prior to, and initially independent from,* genetic causation/dynamics/accommodation/inheritance.
- Second, due to an inherent transitional moment of *instability* during such a discrete or robust transition or 'flip' from one

ESS-state/compromise towards another one, the latter may be vulnerable to, and hence *assimilate*, a 'selfish intruder' or 'invader' which – at the intra-genomic level – may be a new mutation, a previously unexpressed gene, or a selfish and/or mobile genetic element. As such, the model would evolutionary-genetically predict and elucidate:

  - the process or phenomenon of 'genetic assimilation';[78,79]
  - cases where IGC has causal effects on epigenetic-developmental evolution and speciation due to intruding/invading selfish genetic elements (e.g., due to meiotic drive, transposons, selfish driving chromosomes, nuclear-cytoplasmic drive, and so on).[41-48]

- And third, due to the *transgenerational persistence or inheritance potential* of intra-genomic ESS-based regulatory states underwriting (heritable) epigenetic-developmental states, there would be no need to call in the concept of extra-genetic 'epigenetic inheritance' as a separate inheritance system independent from genetics:[59] as epigenetic-developmental variation would ultimately rest on intra-genomic combinatorial ESS-based variation, so-called 'heritable epigenetic variation' would *de facto* be 'heritable genotypic variation'.

CONCLUSION AND FURTHER PROSPECTS

Although the above conceptual sketch does not suffice to draw any definitive conclusion on the relationship between evolutionary genetics on the hand and epigenetic and developmental evolution on the other hand, it suggests that further and more in-depth research into an intra-genomic ESS-modelling could lead to promising results that are relevant not only for the fields of molecular epigenetics and evo-devo but also for the broader MS/EES-controversy. If our above suggestion or hypothesis proves correct, then the gene-centered MS-framework should not undergo a 'revolutionary paradigm shift' towards a 'gene-de-centric' framework, but would only require 'refining'. That is, the classical 'coarse-grained' 'inter-organismal' population-genetic MS-framework (that thinks in terms of competition and cooperation among genotypically represented individual organisms that constitute a population) should be enriched with a more 'fine-grained' 'intra-genomic' (nonlinear multiplayer ESS-based) perspective to tackle the evolution of 'intra-organismal' molecular epigenetics and development. The classical 'inter-organismal' evolutionary phenomenology would then only be the 'tip of an intra-genomic evolutionary iceberg'.[28] This conclusion could be supported by the increasingly revealed causal role and significance of IGC in epigenetic gene regulation, developmental evolution and even speciation.[41-48] The concomitant picture would be one according to which cells and organisms are not true 'units of fitness' but rather 'emergent effects' of ESS-based 'compromises' among basically selfish or conflicting genetic interests.[34,36,40] The result would be a much more information-rich picture of the genome than is being acknowledged by anti-gene-centered EES-advocates: the genome would be much more than just a reservoir of genetic elements or 'developmental resources' that can be 'relativized' or 'de-centralized' within the developmental dynamics of the organism as a complex system. Rather, the genome would be, in itself, a *hierarchically organized complex system*, and the cellular organism is its 'emergent phenomenon'. At its most basic or lowest level the genome consists of the four DNA-nucleobases or 'letters'. These are linked together forming genes or genetic elements, i.e., linear pieces of DNA-sequence-specificity, which are the 'words'. However, it does not stop here. Genetic elements or words, in turn, are connected and recombined in all sorts of ESS-based (nonlinear, multiplayer) coalitions and joint ventures, such as GRNs, forming information-rich 'sentences' and even 'narratives' or 'stories'.[36] Due to *combinatorial explosion* – not just among bases or letters, but also among gene-sequences or words, and even among ESS-based coalitions, GRNs, 'sentences' and 'narratives' – the genome might contain well-enough information potential for how to biochemically and behaviorally respond to environmental parameters and resources for the successful biochemical and physiological developmental construction of an organism. That is, the organism would be like 'temperature' or a 'thermal process' – an 'emergent' phenomenon or process resulting from lower-level molecular interactions, here intra-genomic nonlinear multiplayer ESS-based interactions among numerous genetic elements, of which classical 'inter-organismal' evolution only represents the 'macroscopic' tip of the evolutionary iceberg.

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