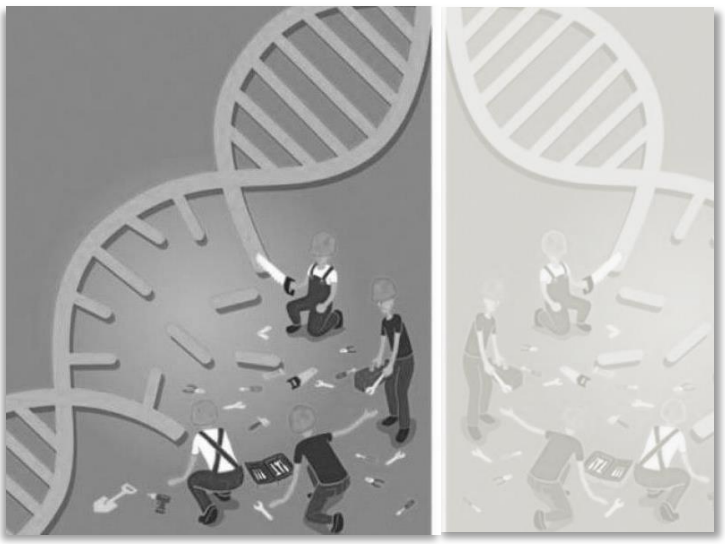

THE SEXES FUNCTION TO PURGE MUTATIONS VIA SELECTION ON MALES, BOOSTING THE ABILITY OF SEX TO MAINTAIN GENOME INTEGRITY

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ABSTRACT:

The function of the sexes is revealed within the context of new understanding that sex maintains genome integrity. Whereas originally evolved features of sex, conserved in early stages of meiosis, repair gross DNA damage, later phases repair fine-scale DNA damage (mutations) via ploidy and the sexes effecting purifying selection. Rather than in anisogamy, the (proto-)male arises in mating-types, revealing that greater selection on the male is the male's defining characteristic; this is confirmed in experiment and modelling. The variation theory ignores all evidence from many fields that it's asexual reproduction that produces variation. Recent tests unwittingly support the genome-integrity model. The profundity of male/female distinction in differential selection prompts new understanding of sociality and psychology in sex-specific terms.

Key words: function of the sexes, selection on the male, purging mutation, genome integrity, DNA repair

INTRODUCTION

The question of what is the function of the sexes (males and females) is a subsidiary one to that of the function of sex (sexual reproduction), but of course the sexes would be expected to support the overall function of sex, and, indeed, to be very much part of it. Sex occurs in lowly species with no male/female distinction, and sex without sexes is the ancestral state. With the sexes evolving in the wake of the emergence of sex, it would be instructive first to look at the evolutionary origins of sex, yet this is an endeavour mostly eschewed by investigators as supposedly not open to study. Experimental work on sex has focused on trying to understand its maintenance, leaving its initial function an entirely separate supposedly unfathomable question, but such work is liable to ignore -- although being based on -- the very assumptions about the function of sex at issue. Instead of this artificial divide, a good starting point for investigation would seem to be a dissection of meiosis into its component parts, right from its initial phase, to delineate functions, both overall and in its subsidiary aspects. Fortunately, analysis of sex into separable, successive stages is now quite advanced. Albeit that the sequence of phases of meiosis does not necessarily reflect the order in which they evolved, the general direction of any shifts in function should indicate or at least give clues to the reason why the sexes then emerge.

THE PHASES OF MEIOSIS REVEAL THE REPAIR FUNCTION OF SEX

It is well established that oxygen -- 'reactive oxygen species' (RAS) within the cell -- damages DNA (eg, Hemnani & Parihar, 1998). That it is this problem that the evolution of sex solved is shown by Nedelcu & Michod (2003) and, most recently, by Hörandl & Speijer (2018). RAS, produced by metabolism, rise to ever more increasingly problematic levels as metabolic rates speed up with organismal complexity, and notably with the energy demands of predation. This issue was addressed very early in evolutionary history when very primitive species evolved through symbiotic capture of another organism, which thereby became an endosymbiont -- a new organelle within what remained a unicellular species (this being the origin of the cell's energy-producing organelle, the mitochondrion: from a precursor proto-mitochondrion, once free-living bacterium).

The damage sex addresses is either grossly to the overall structure of DNA (such as breakages of strands or contortions of the topography of such a complex molecule as to constrain its protein chemistry), or more finely to the sequencing of bases comprising genes

(mutations); the former making the latter more likely. DNA structure has to be repaired, otherwise the damage would prove lethal. Mutations, by contrast, are very small, discrete elements that may possibly accumulate to the point of lethality or sterility, though more usually a mutational load leads to reduced reproductive output (in quality/quantity). To varying degrees, deleterious genetic material is eliminated through not being inherited by offspring: by purging or purifying selection (both terms being used in biology, more or less inter-changeably).

It would be expected, then, that the more indispensable and earlier evolving aspects of sex would be concerned with macro-level DNA repair, and this indeed turns out to be the case. Mirzaghaderi & Hörandl (2016) find that the stages within the initial part of meiosis known as Prophase I (homologue pairing, double-strand break formation and strand exchange) are all concerned with accurate copying of properly (re)constituted whole chromosomes. These mechanisms reveal themselves to be vital in being invariably conserved throughout evolution, whereas other elements of meiosis (crossing-over formation and recombination) are not.

The next most indispensable element, as would be expected, deals with micro repair: by ploidy – chromosomes carrying the same genes being paired (diploidy) – whereby the expression of deleterious mutations can be reduced in their having to be paired up with a different version of the same gene (an allele) in the diploid form. Unless the mutant allele is dominant, it won't be expressed. Unlike the former stages, this one can be skipped for several generations (as in species that thereby are dubbed facultative rather than obligate in their sexual reproduction).

Bringing up the rear, as the process that is under least selective pressure, indicating that it's the most dispensable element, actually is what is usually most associated with sex – out-crossing recombination. Indeed, as Mirzaghaderi & Hörandl point out, variability in offspring *actually works against* the other, far more important mechanisms in sex.

SEX DID NOT EVOLVE TO PRODUCE VARIATION, BUT TO MAINTAIN GENOME INTEGRITY

This DNA repair primary function of sex, with the variation produced by out-crossing recombination an incidental by-product, is not a brand-new insight. It was outlined by Bernstein, Bernstein & Michod (2012), and in several papers after originally being formulated as long ago as 1977 (Bernstein). In a review, Gorelick & Heng (2011) build on extensive earlier work

by Heng to spell out the profound implications of sex being concerned essentially with DNA repair: that sex functions to maintain the integrity of the genome (the genome and not the gene being the true information unit on which selection acts -- as is outlined here in later sections). It's only at the micro-evolutionary level where is allowed variation, that, therefore, is but minor, being just an unselected by-product of sex. A relatively insignificant mere hitch-hiker (an epiphenomenon) that occasionally may possibly allow new adaptation through a rare beneficial mutation arising and being disentangled from other genes on the same chromosome – what has been dubbed the ruby-in-the-rubbish argument (Peck, 1994).

Further elaborating this perspective, Gorelick & Villablanca (2018) explain that crossing-over recombination, rather than being the hallmark of sex, is instead the result of imperfect error correction – collateral damage caused by breaking up co-adapted gene complexes, which is known as recombination load. Though this does occur in meiosis, it is a far greater problem in mitosis (asexual division), and, therefore, there is vastly more variation produced in *a*sexual compared to sexual reproduction. This completely contradicts the claim of the variation theory of the function of sex.

The hitherto long-standing predominant view that sex serves to produce variation, Gorelick & Heng explain, stems from a major misunderstanding from over a century ago by Weismann (1891), that meiosis increases not only variation at the level of the gene (which it does) but also at the level of the chromosome (which it does not); Weismann failing to see that in meiosis one copy of each homologous chromosome is passed on to each daughter cell. The upshot of this misunderstanding is that the amount of variation produced by sex has long been hugely over-estimated: quantified by Gorelick & Villablanca (2018) as out by a factor of the order of 100,000. That there has been such a ready, enduring, uncorrected acceptance of this mistake is because major theory by Darwin (1859), as built upon by Fisher (1930), required a recurring reservoir of genetic variation. This profound mis-reading has persisted despite there being not only no convincing evidence in favour, but – as Gorelick & Heng stress – *all* of the evidence from many scientific fields (ecology, paleontology, population genetics, molecular biology and cancer biology), that sex overall actually *decreases* genetic variation in acting to conservatively filter out any major changes so as to preserve the integrity of the genome. This is a very large set of converging lines of evidence that no scientific investigation of the origin of sex should ever

ignore, yet ignored it has been.

That the role of recombination is only to effect minor changes at the genic level shows up in sexual populations not adapting or doing so at a much slower rate than expected (Futuyma 2010), such that sex never would have arisen at all if its function were to produce variation, given that asexuality produces much more of it. This is as previously confirmed by Heng in his review of data in the literature, strongly supporting a reinterpretation that "the principal consequence of sexual reproduction is the reduction of drastic genetic diversity at the genome or chromosome level, resulting in the preservation of species identity rather than the provision of evolutionary diversity for future environmental challenges" (Heng, 2007, abstract). Sex actually "slows (constrains and restrains) evolution, enabling lineages to conservatively defer extinction. … sex is a brake, not an engine, of evolution. … (or) like a clutch, most of the time sex causes almost no change and, in fact, limits the speed of evolution to some narrow band" (Gorelick & Heng, 2011, p1096).

The genome-integrity hypothesis, however, albeit gaining ground, has not overtaken the generally accepted explanation of the origin of sex. With the perceived need for a reservoir of random genetic mutation upon which selection can act to bring about evolutionary change being undiminished, papers continue to be published purporting to uphold the variation theory.

THE MOST RECENT SUPPOSED EVIDENCE FOR THE VARIATION THEORY IS ANYTHING BUT

These actually undermine what they purport to bolster. It would appear that the heavy investment by some researchers in the status quo prompts interpretation of results from experiments as supportive of the variation theory when instead it is the 'genome integrity' hypothesis the data fits. Indeed, the rival hypothesis is not even considered as an alternative. Research is concerned simply with endorsing the variation theory vis-a-vis the null. This profound bias appears very much to be the case in the most important recent work on the origin of sex: McDonald, Rice & Desai's (2016) pioneering genomic sequencing study of how sex may work at the molecular level, and in Sharp & Otto's (2016) analytical review of it. Yet the key empirical finding of the study actually is re purging:

> *Recent theory has argued that the fixation of strongly deleterious mutations can be common in adapting asexual populations. Our results provide the first direct experimental support for this hypothesis. In contrast, recombination decouples hitch-hiking mutations from their initial background, and we identify no deleterious mutations that fix in sexual populations. (McDonald et al p. 234).*

Instead of this being the main conclusion in the abstract, it is downplayed as a subsidiary finding; McDonald et al preferring instead to state in the final sentence that: "Our results demonstrate that sex both speeds adaptation and alters its molecular signature by allowing natural selection to more efficiently sort beneficial from deleterious mutations".

In the previous sentence, they relegate their principal empirical result to the status of a mere additional finding: "We *also show* that substantially deleterious mutations hitch-hike to fixation in adapting asexual populations. In contrast, recombination prevents such mutations from fixing" (my italics).

The paper is titled *Sex speeds adaptation by altering the dynamics of molecular evolution*, but more accurately would be titled *Sex slows maladaptation*.

The principal empirical finding is picked up by Sharp & Otto, who, furthermore, anchor the remarkable quantitative difference between sexual and asexual reproduction with respect to deleterious mutation:

McDonald et al were able to establish that selective interference was substantial in the absence of sex: several deleterious mutations rose to high frequency in the asexual populations through hitch-hiking with beneficial mutations, as seen previously. By contrast, in sexual populations, deleterious mutations that began to spread were uncoupled from beneficial mutations during subsequent rounds of recombination and then declined in frequency. As a consequence, less than a quarter as many mutations reached high frequency and fitness rose almost twice as much in the sexual populations. (p. 754)

In the following sentence, furthermore, Sharp & Otto make it clear that any benefit conferred by sex in respect of beneficial mutation is merely a *subsidiary* issue: "*In addition*, McDonald et al observed that sex allowed new beneficial mutations to combine with alternative alleles maintained by frequency-dependent selection, allowing for selective sweeps without disrupting a stable polymorphism" (my italics). Yet Sharp & Otto go on to mislead in their review

after the manner of the authors of the original study. Despite the principal finding of McDonald et al pointedly elucidated by Sharp & Otto as being that *deleterious mutations are more than four times less likely to reach high frequency in sexual compared to asexual populations*; they concern themselves instead with the recruiting of beneficial ones. Rather than focusing on the striking conservation conferred by sex in purging deleterious mutation, Sharp & Otto categorically state as their conclusion: "we can say definitively that sex reduced selective interference, uncoupling beneficial alleles from the deleterious alleles in their genetic background" (p.758). So just as did McDonald et al, the authors fail to properly summarise the findings and go so far as to make an unwarranted claim in highlighting the merely additional whilst ignoring the principal result. This is misleading by major omission. If "uncoupling beneficial alleles" is seen merely as an ambiguous phrase, in that the corollary is likewise uncoupling of deleterious alleles; there is no mistaking the intended message. Sharp & Otto appear to be concerned only with trying to support the failing ruby-in-the-rubbish theory of sex, pointedly contradicting the claim of the title of their paper, *Evolution of sex: using experimental genomics to select among competing theories*.

Jaffe (2018) not dissimilarly appears to succumb to confirmation bias and views sex in this heavily distorted fashion: as primarily to "conserve alleles that might be useful in the future". This is to fail to point out even as a possibility that his "test" that alleles undergo in sex, is to weed out the vast bulk of mutation as the deleterious material it is. In common with some others of the 'variation' camp aware of the deficiencies of the theory, Jaffe backtracks to call for a pluralistic model. Most recently in defensive retreat there has been invoked severe ecological interactive complexity (Good et al, 2017), which a commentary in the same journal issue has dubbed (in reference to Darwin's famous phrase), *the tangled bank* (Plotkin, 2017). In the same vein, Luijckx et al (2017), in their paper, *Higher rates of sex evolve during adaptation to more complex environments*, seem merely to assume that variation and selection to fixation of novel beneficial alleles underpins their findings, as if there were an absence of a competing hypothesis, never mind that the hypothesis that sex maintains genomic integrity would not merely explain their findings just as well, but better. With asexuality actually more able – far more able – to give rise to variation than sex, then, on the variation hypothesis, sex ought to evolve *less* in the face of complex environments, not more.

These papers present no effective defence of the variation theory. It is not just that in trying to rescue an ailing theory it is anyway compromised in the lack of parsimony. Complexity serves to hide from scrutiny, and data then becomes much more ambiguous as to interpretation at the very juncture when testing to exclude an alternative hypothesis has become especially necessary.

THE-RUBY-IN-THE-RUBBISH POSITION WAS ALWAYS FLAWED

These authors entirely ignore, first, that the "genetic background" is hardly the relatively tiny total number of new mutations they cite (even including their gene neighbours from which they have to be disentanged). Rather, it's the long-evolved well-functioning whole genome, whereby the inter-connectivity of all genes means that selection acts on the organism as a whole; on overall condition (the now fully confirmed notion of genic capture: see the section below on sexual selection). They ignore, second, that with the vast majority of mutations being deleterious, the main supporting function of sex is purifying selection (purging). It is perverse to be concerned instead merely with the shadow possibility that the small amount of residual, potentially non-deleterious mutation, may then have a better chance of being in a context to be beneficial and thereby to fix. In eschewing, in the face of evidence and argument, any cognisance of sex as conservation in favour of considering it as a means of facilitating new adaptation, there would appear to be confirmation bias in the extreme.

Adherents of the ruby-in-the-rubbish position appear to fail to appreciate that populations facing environmental change threatening local extinction would be expected to have only an extraordinarily low chance that a recent mutation or novel genetic recombination (even assuming it could be disentangled from its chromosomal cohorts) might accidentally confer on an individual some protection sufficient to engender changes in just the right way as to weather the storm. Instead, it would be anticipated that, with the reproductive group maintained at an optimum or near maximum fitness through purifying selection, there might be some chance of a few either statistically outlying or particularly optimised individuals managing to hang-on, even as the rest of the population succumbs. We know that the highly competitive nature of males combined with the highly choosy nature of females can weed out from reproduction even high-functioning (in not being the high*est* functioning) individuals in a zero-sum game that tends to (though doesn't fully) become a runaway phenomenon, with males indicating their fitness via

what has been termed costly signalling. In this way, the male is constantly pushed to maximise all of his qualities in conjunction (that is, not to the detriment of, if not synergistically) with each other; just as is needed, in readiness for threats to local extinction, whether recurring and thereby anticipated or hitherto unseen, to perennially hone the gene pool. [Note that there is no introduction here of inappropriate notions of group selection; the stale debate on that topic having resolved into several empirically equivalent theoretical positions, and not just multi-level selection, satisfactorily explaining mutualism: see referenced discussions in several of the present author's papers.] This fundamental and highly robust mechanism of evolution surely dwarfs the minuscule chance of random beneficial mutation in its potential for avoiding local extinction.

Also clouding matters is the mistaken notion that for the variation theory to be challenged it needs to be demonstrated that there is some other, single benefit to fully offset the two-fold cost of sex (from considering that the asexual mode achieves double the rate of reproduction, in that both parties give birth, not just one of them). On this basis, purging has been deemed to be inadequate, but through failing to acknowledge that purging is only a subset of DNA repair mechanism, and is the function not of sex per se but specifically of the sexes. The cost of the sexes is offset not just by the benefit of purging (micro-level DNA repair) but also by the benefit of macro-level DNA repair, given that the latter already is apparent in sex before the sexes emerge. The test for purging, therefore, is only to explain the additional cost of the sexes, not the additional cost of sex per se: the cost of the sexes minus the benefit of sex. Thus is left far less to account for than a two-fold cost differential. Consequently, data falling short of showing that sex is twice as efficient as asexual reproduction cannot be dismissed as failing to challenge the variation theory. In any case, that purging *even on its own* renders sex more than twice as efficient as asexual reproduction is shown by Lumley (2015).

Notwithstanding attempts to uphold and defend the variation hypothesis, then, this hitherto predominant view appears set to change towards a new consensus on sex as assuring genome integrity, in the manner of a paradigm shift. The next question, is how do the sexes serve the overall function of sex of assuring genome integrity? Arising as they do in the wake of the later phases of meiosis that address the problem of repairing not macro-level but micro-level DNA damage, the expectation is that the sexes would further contribute to this, by dealing with deleterious mutations.

ANISOGAMY IS NOT THE ORIGIN OR INITIAL MANIFESTATION OF THE SEXES

In any account of the origin of the sexes, it is necessary to specify what the sexes are at root, instead of simply assuming that they are distinguished by size (and/or number) disparity of sex cells (gametes), as the sexes usually are defined. As has long been recognised, evolutionarily prior to any male / female distinction, and before germ-line sequestration (the separation of gametes from somatic cells, instead of the individual and the gamete being one and the same), individuals / gametes are indistinguishable morphologically or in any way phenotypically. This is the case for some extant species, very many extinct, and, it is presumed, ultimately for the common ancestry of all species. It's a condition dubbed *isogamy*, meaning literally *equal marriage*, but with the more specific meaning in biology of equal-*sized gametes*; as opposed to *anisogamy*. It might be thought that the sexes arose through polarisation in size of formerly same-sized gametes / individuals, but the question is begged: what drives this? It must have a genetic basis, so how did this arise? A dominant theoretical position has been that anisogamy is the result of intra-genomic conflict, but, again, such conflict ensues from a genetic difference that indicates or is in itself some prototypical form of the sexes, so can hardly account for their emergence. The same applies, self-evidently, to a similar hypothesis of parasitism of one gamete form on another. However, far from one gamete form being advantaged at the expense of the other, models reveal that anisogamy produces increased fitness for both.

Roughgarden & Iyer (2011) show that anisogamy evolves if large zygotes are favoured and the difference in gamete sizes maximises the rate at which gametes encounter each other, and hence the number of zygotes produced. This is also the conclusion of Lehtonen, Kokko & Parker (2016) in the most recent review of the topic. They point out that isogamy becomes evolutionarily unstable if gametes have difficulty finding each other (as when they are at a distance). Here, by reason of the need for greater efficiency, populations evolve into two specialised complementary subsets of majority small motile searcher gametes (microgametes) and minority larger, sedentary gametes (macrogametes). The far lower investment required in microgametes means that the wastage cost of their being in surplus is insignificant in comparison to the benefit of the additional search capacity (reducing the time to and uncertainty of gamete fusion – syngamy) through their much greater number. The alternative -- a uniform set of medium-sized, merely semi-motile gametes – would entail all of them being average-to-poor in search ability, leading to a lower total number of syngamous sex cells (sex

cells fused with another in a zygote) and a longer time taken for all pairing-up in syngamy to be completed. Note that size disparity between subsets of gametes also makes sense in the evolution from unicellular to multicellular species, and more generally with increasing adult mass. The problem of the vulnerability and dependence of the sub-adult in the prolonged period of growth of the zygote, to an extent can be ameliorated by its possessing a sizeable complement of nutritional resources contributed by the macrogamete, and thereby already being large at the outset of development.

Lehtonen, Kokko & Parker neatly explain that anisogamy becomes in effect an evolutionary valve, with even low levels of (what we might call) sperm competition usually preventing any reversion to isogamy:

> *As soon as gamete sizes have diverged and one gamete type outnumbers the other, many gametes of the more numerous type (sperm) are destined to remain unfertilized. Because it is not known in advance which male gametes will be successful, a relatively small increase in the reserves of the few successful sperm would require wasting the same amount of extra provisioning on a large number of unsuccessful sperm. On the other hand, even a relatively large change in the size of a tiny sperm can still be very small in relation to the size of the egg, therefore contributing little to the survival of the zygote. The result is that increasing zygote provisioning by a significant amount requires a large decrease in micro-gamete numbers, with a corresponding decrease in sperm competition ability. (p. 1165)*

Conversely, anisogamy drives competition between sperm (that is, male individuals: there is no distinction at this phylogenetic level between somatic and sex cells; there being just a single cell), in that the more numerous form of gamete has far more scope to increase fertilisation probability. Therefore, it becomes adaptive to evolve mechanisms to compete – in more evolutionarily advanced organisms, between somatic individuals as well as between their sex cells (and both before and after ejaculation). The question, though, is whether or not a size divergence begins spontaneously – by a chance initial distinction, or through some incidental process – or if there is already a distinction between two forms that in turn provides the basis of an ensuing morphological split. It turns out that it is the latter. *Isogamy* is a misnomer. That is, *isogamy* defined in terms of not just size but any sort of apparent (phenotypic) difference is a misnomer.

This is the issue for any and every hypothesis proffered for the origin of the sexes if it is

presumed that it is entailed in the change from isogamy to anisogamy. Da Silva (2017) puts forward a game-theoretic conceptualisation of competition among gamete-size alleles within mating-types, which model he classes with others in the category of disruptive selection, contrasting (as da Silva sees it) with those in terms of gamete limitation (or intra-cellular conflict). Lehtonen, Kokko & Parker's paper isn't cited – presumably, at the time of writing it was still to be published. Although da Silva may have a viable rival explanation for the onset of anisogamy, it hardly befits his title, *The evolution of the sexes*. The mistaken assumption that "gamete dimorphism … defines sexes" is stated in the first sentence of the introduction. As da Silva himself outlines, prior to the sexes there are mating-types. And like sexes, mating-types, as the very term for them denotes, are different, with all individuals being either of one or of the other of two complementary forms. Mating-types appear to be sexes in all but name.

THE SEXES BEGIN AS MATING-TYPES, DISTINGUISHED NOT PHENOTYPICALLY BUT GENETICALLY

The seemingly all-identical isogamous gametes, albeit morphologically (re form or structure) and in any other respect phenotypically (re observable characteristic) indeed indistinguishable, nevertheless differ genetically. Invariably, isogamous gametes are actually of at least (and usually) two contrasting, complementary mating-types, denoted + and -, which can mate only between and not within type. Note that these are not gamete size alleles as proposed by da Silva, which would be derivative. Consequently, discussion of the locus of the emergence of the sexes has to shift from anisogamy to mating-type. With the presence of different mating-types, isogamy plays host to what can be termed sexual or proto-sexual selection *before* there is any anisogamy. So it is not the transition from isogamy to anisogamy that is key to understanding the basis of the sexes, but in how mating-type arises.

That the emergence of anisogamy from isogamy is of no import to the origin of sex is now evident in molecular research. Hamaji et al (2018) show that the shift from mating-type to sexes is effected by a tiny initial change in just one of the two small genes determining mating-type, confirming the finding by Geng, De Hoff & Umen (2014) of a very simple genetic continuity between mating-type determination and sex determination. The two sexes emerge before any phenotypic sexual dimorphism. Males and females begin as isogamous. Anisogamy truly is derivative: the product of differentiation by sex rather than its cause.

The phenomenon of mating-type most recently is comprehensively reviewed by Hadjivasiliou & Pomiankowski (2016), who conclude that it cannot have arisen through any hypothesis hitherto proposed. Those concerning in-breeding avoidance and uni-parental inheritance of cytoplasm functioning to purge mitochondrial DNA mutation (see below) or (so-called) selfish elements both fall, since instances of in-breeding and bi-parental inheritance can occur notwithstanding the presence of a mating-type system. Instead, the authors follow up the work by Hoekstra (1982) on mating-type as signalling between gametes (which they find to be universally asymmetric and necessarily so) for prospective partner recognition and pairing. Otherwise, with all gametes issuing the same molecular signature, then given the nature of chemical diffusion, a gamete's receptors would be swamped by its own secretions of identifying / advertising proteins, rendering it incapable of detecting those emitted by a potential partner gamete. Gametes would never be able to attract and locate each other. The authors have now gone on themselves to fully model the emergence of gamete signalling (Hadjivasiliou & Pomiankowski, forthcoming).

With (usually) an initial disparity in number between different mating-types, those of the less numerous type will more easily successfully mate (fuse with those of the other, *more* numerous type in syngamy) than those of the more numerous type. Hence, the rare gametes still available for mating decline disproportionately, and therefore the task gets progressively harder to identify, locate and approach them. Consequently, the probability of any one individual of the more numerous mating-type remaining un-mated increases. This sets up a selection pressure on the more numerous mating-type to mate early. From what may be initially an almost negligible difference that arises by chance or for some incidental reason, a polarisation naturally ensues whereby one of the mating-types is then obliged to make more effort than the other, which, over time, becomes ever increasingly the case – a runaway phenomenon of increasing competitiveness.

In this it might be thought there is the very beginnings of competitiveness being a quintessentially male trait (Moxon, 2015), and that herein is the defining male characteristic. However, competitiveness is the corollary of greater selection, and with selection pressure being the underlying driver, then it seems that the male (or proto-male) is best defined in terms of selection rather than competition. The mating-type subject to the greater selection therefore in

principle would be the one deemed *male* or *proto-male*.

A model based on this simple logic of inevitable skewing, Hadjivasiliou & Pomiankowski claim, is superior to previous hypotheses, in being applicable to all of the various mating-type systems seen in nature. It's a model of parsimony, requiring nothing antecedent, being, as it were, a pure first cause.

HYPOTHESES IN TERMS OF MITOCHONDRIAL DNA ARE LEFT WANTING

One (or a more specific version of one) of these previous hypotheses has been put forward by Radzvilavicius (2017) as a unified theory to explain the origin of sex and its developments (notably a separate germ-line): that this is the result of the need to deal with mutation in mitochondrial DNA. [Mt DNA, unusually for DNA, is not in the cell nucleus but the cytoplasm: within the mitochondria themselves – see further discussion below.] This again goes against the simple model of the asymmetry of mating-type arising by chance, but the claim is anyway a weak one: "… mitochondria *could* have represented *one* of the driving forces behind the origin of sexual life cycles" (Radzvilavicius, 2017 p37 – my italics). In other words, in order to account for the origin of sex, the proposed need to deal with Mt DNA mutation is neither necessary nor sufficient.

The question had already been settled by Hadjivasiliou, Lane, Seymour & Pomiankowski (2013), who conclude in their abstract that "*only when two mating-types exist beforehand* can associated UPI (uni-parental inheritance) mutants spread to fixation under the pressure of high mitochondrial mutation rate, large mitochondrial population size and selfish mutants" (my italics). This finding is not new: as the authors themselves point out, it echoes that of Hastings (1992), and serves to undermine all of the Mt DNA hypotheses – including the original one by Nick Lane (Hadjivasiliou, Pomiankowski, Seymour & Lane, 2012), about a supposed need to co-ordinate between the different complements of mitochondria-controlling DNA in the cell cytoplasm (ie, within the mitochondria themselves) and in the cell nucleus.

Furthermore, new thinking from the Nick Lane camp is that purging Mt DNA mutation does not, after all, drive the emergence of the two sexes in the wake of the sequestration of a dedicated separate germ-line (tissue with the sole function of producing gametes, distinct from normal, somatic cells). It is now realised that it is the other way round: the emergence of the

sexes is a prerequisite for a separate germ-line to evolve. Radzvilavicius et al (2016) conclude (p 3) that: "germ-line sequestration is plainly a secondary adaptation — uni-parental inheritance and oogamy arose before oocyte sequestration in early development, and the evolution of two sexes cannot simply be a matter of protecting template mitochondria" (oogamy being the phenomenon of very large oocytes – eggs).

The upshot is that the various previous Mt DNA mutation hypotheses and the new, mating-type (what might be termed) chance-change hypothesis of the origin of the sexes are neither in competition nor account for overlapping phenomena (or different aspects of the same phenomenon), but describe two different successive parts of a *sequence*. The chance-change phenomenon arises first, inevitably providing scope for differential selection, and thereby the evolution of the second phenomenon, a mechanism to deal with Mt DNA mutation, perhaps initially in the form of a / the major aspect of mating-types / the sexes. In other words, the natural occurrence of a small degree of asymmetry is recruited by the evolutionary process to serve the function of dealing with an emerging problem; namely, the accumulation of Mt DNA mutations. Mating-types / sexes came first, with mechanism to deal with Mt DNA mutation a subsequent development. But this is not to say that this latter development is unique in dealing with mutation, nor even necessarily the first such mechanism. It may be a sub-set of much wider purging. If the sexes can be shown to serve to purge mutations of one particular part of the genome, then the suspicion must be that this is a more general principle, and that the sexes serve to deal with the mutational load of the genome as a whole. As this anyway is what is emerging from mounting evidence as set to overturn the variation theory, then the hypothesising about Mt DNA becomes an additional line of evidence in that regard.

SELECTION IS THE UNDERLYING PRINCIPLE

To reiterate and expand: from the onset of differential selection according to mating-type, the corollary of competition manifests as the generic male characteristics of motility and search, and then wider forms of male intra-sexual contest. So the origin of the male-female distinction is not the size difference in anisogamy (the notion of the female always being the larger gamete), nor the related supposed basis of distinguishing the sexes in terms of investment – that females always invest more in offspring than do males. [In any case, there is doubt as to whether or not this invariably holds. There are apparent exceptions whereby the male may be the overall greater

investor in offspring. In ground-nesting birds there is far greater predation on the parenting bird, who is already exposed on the ground and even more so in trying to defend its highly vulnerable offspring. This makes it impossible for the female, as the limiting factor in reproduction, to perform this function. It is not a case of males taking on the female role per se, but of males being obliged to extend their intra-sexual competitiveness into what usually would be a female domain, because females have defaulted to their core reproductive function. The female still invests heavily in offspring (in gestation), but it may be that by some measures this investment is outweighed by the need for that which is loaded on to the male.]

Both greater size and greater investment by the female are derivative; just as are male motility, the facility to search, and competitiveness itself. All are derived from a natural concomitant of assortment: a random or incidentally caused disparity in numbers inherently entailing differential selection. The basis of the origin of the sexes is, simply, *selection*; selection acting disproportionately on what thereby would be deemed the (proto-)male.

The significance of this is that from this unimportant slight difference, the opportunity then arises for the evolutionary process to recruit this male-biased selection as a vehicle for off-loading accumulating mutations (almost all of which, it has long been recognised, will be deleterious – synergistically so: at best mildly deleterious rather than neutral). This is purging or purifying, through selection acting predominantly on the male. Thus, the female is spared to focus on and invest in reproduction, and thereby to become increasingly the limiting factor in reproduction. In turn, the male is required to be ever more subject to sex-differential selection, in a ratcheting-up to polarise the sexes. This would be expected then to drive the evolution of mechanisms in effect to quarantine deleterious mutation on the male side of the lineage in readiness to be purged, by such mutation being more expressed and/or more exposed in a male context.

There are several mechanisms at work here. It is now known that there is far greater inheritance of male genetic material that actually is expressed, through a process as yet not understood together with so-called 'imprinting' (an allele is 'tagged' as being from the male parent and when it's transcribed in offspring the tag renders it dominant to other alleles), creating a large skew in favour of male-derived alleles (Crowley et al, 2015). Competitiveness in males is in itself the key mode of both expression and exposure, which drives the male sociality

of hierarchy (dominance and/or prestige), ranking males in terms of genetic quality, to then be subject to female choice. Another mechanism would be the male being the heterogametic sex: the one with different (X & Y) rather than identical (X & X) sex chromosomes, so that sex-linked alleles are exposed singly instead of being masked by its opposite number on the parallel chromosome. Yet another is evident in respect of the afore-mentioned Mt DNA, which, with its DNA unlike any other in being contained within the organelle itself, can be purged of accumulated deleterious mutation by excluding male mitochondria from the zygote, leaving all Mt DNA replication to be from mitochondria within female gametes. This is a simple, extreme mechanism whereby *all* Mt DNA mutation within males is eliminated. The necessity of this is because Mt DNA is much more susceptible than other DNA to error (structural damage and mutation) through the products of respiration (energy production) such as free radicals -- mitochondria being the organelles responsible for respiration -- and there are a very large number of cell divisions in spermatogenesis compared to oogenesis.

Replication in the course of human spermatogonial stem cells begin (mitotic) division from the onset of puberty at the rate of one every sixteen days, so that the sperm of men by their 64th birthday are the product of 1,152 divisions. By complete contrast, ova (oocytes, eggs) are produced pre-natally almost complete, having undergone not even a single meiotic round – just part of the first of a mere two meiotic divisions required for the final production of the egg. This first is held in abeyance as the ovum is simply stored until ovulation, upon which meiosis is resumed, to complete meiosis I and then meiosis II. Nevertheless, with necessarily still some iterated replication (as with sperm, over 30 mitotic divisions before meiosis begins), then inevitably is entailed significant accumulation of mutation, albeit a very small amount in comparison to what would occur in male gametes. Consequently, in a process known as atresia, ova are subject to attrition during maturation, such that any eggs with a significant Mt DNA mutational load are discarded, in the human case leaving only 10% to achieve viability. (eg, May-Panloup et al, 2016). So here the female takes on what is normally the male role of 'genetic filter', though the 100% elimination in the male in effect trumps the 90% purging in the female. It could be considered that the rule of more selection acting on the male is invariable, or that the case of Mt DNA is the exception that proves the rule. Either way, overall, with the vast bulk of purging occurring in the male, the principle holds that differential selection according to sex defines *male*.

EVIDENCE OF DELETERIOUS MUTATION REQUIRING EXTRA SELECTION ON THE MALE

The generality that overall selection acts much more on males than on females has long been regarded as obvious and not an empirical question. Yet when the notion of purging via the male being the very function of the male and why the male arose was put forward by Wirt Atmar (1991) in his concept of the male genetic filter, it was ignored. Despite publication in the leading journal, *Animal Behaviour*, there are just two citing authors other than the present one. It seems to have been an innovative hypothesis too far, against the grain of contemporary theorising about sex. West-Eberhard (2005) entirely independently (and seemingly in ignorance of Atmar) originated the very same analysis of the male functioning as what she termed the mutational-cleanser. This was or should have been harder to ignore, given, by then, Siller's (2001) modelling that the far greater differential in reproductive output among males through competition over mating serves to purge deleterious mutation, even whether or not there is epistasis (synergistic interaction between genes); and similarly Agrawal (2001) showed that if mutations are more deleterious in males then the extra selection on males could eliminate the cost of sex (and, again, irrespective of epistasis). On top of this modelling had come evidence that selection acting on males removed experimentally induced mutations to the extent that it indicated the likelihood that purging could offset the two-fold cost of sex (Radwan, 2004). That there is always more selection on the male half of the lineage across all loci was found in indirect evidence by Whitlock & Agrawal (2009), then a review of comparative genomics projects revealed in direct evidence that selection was always stronger on males (Singh & Artieri, 2010); this being confirmed across the animal kingdom by Janicke et al, 2016 -- Janicke et al (2018) most recently finding that this prevents species extinction (though the authors remain open-minded as to the mechanism). That greater selection specifically on males results in reduced mutational load has been demonstrated experimentally by, for example, Mallet et al (2011: *Experimental mutation accumulation on the X chromosome of Drosophila melanogaster reveals stronger selection on males than females*), McGuigan, Petfield & Blows (2011: *Reducing mutation load through sexual selection on males*), Harrison et al (2015: *Sexual selection drives evolution and rapid turnover of male gene expression*); most recently, Noël et al (2019: *Sexual selection and inbreeding: Two efficient ways to limit the accumulation of deleterious mutations*).

There is abundant evidence, then, from both experiment and modelling, that invariably selection acts more on males than on females, clearly showing that this is a defining basis of the

distinction between the sexes. Confidence in this conclusion is increased still further with the significance of sexual selection to the emergence of sex as an improvement on asexual reproduction.

SEXUAL SELECTION IS CORE TO WHY SEXUAL ECLIPSED ASEXUAL REPRODUCTION

Roze & Otto (2012), in a simulation of an analytical model to precisely quantify effects, find that sexual reproduction evolves in preference to *a*sexual if deleterious mutations are purged more through males, *irrespective of any purgation through females*, including if there is *no selection through females at all*. This makes sense in that females overall are fitter than males and gain further in fitness from selection on males producing their (what have been dubbed) sexy sons (who provide their mothers with more and higher-genetic-quality grandsons).

It is sexual selection that cements sex to evolve to be more than occasional among cycles of asexual reproduction (facultative sex), instead becoming obligate (invariable, with no asexual interludes) (Kleiman & Hadany, 2015). The seminal finding here is that obligate sex displaces facultative sex even if the average fitness of offspring is reduced. This is because of the far greater reproductive success of obligately-sexual males: the large reproductive skew among males that sexual selection achieves – even to the point where a single very-high-genetic-quality male could impregnate all females within the local reproductive group.

That sexual selection is key to sexual reproduction is experimentally demonstrated and explained by Lumley et al (2015), who find that lineages previously featuring sexual selection are twice as resistant to extinction – they survive for twice as many generations – compared to those which had been absent sexual selection. This is the result of *genic capture*: the understanding that with genes providing mutual context to one another, competition between males leading to success in being sexually chosen depends on all aspects of an individual's condition. In this way, sexual selection acts on all the genes of the genome, driving considerable variance in male reproductive success, with even the average father carrying a much-reduced mutational load compared to the mean across all males. Hitherto it had been assumed that purging takes place only at certain loci where there is synergy (greater than merely additive combined effect) between deleterious mutations, and that unless this purging is particularly strong (to make up for the absence of such synergy over the great bulk of the genome) the conclusion would be that there is insufficient purging for sexual selection to be of significant benefit. Studies focusing only

on such a restricted understanding of genetic synergy are bound to lead to under-representation of the impact of sexual selection. Lumley et al show that through genic capture sexual selection across the whole genome is so powerful that it is more than enough to compensate for the so-called two-fold cost of sex – though see above why this anyway is not necessary. The reality of genic capture at the molecular level finally has been established (Dugand, Tomkins & Kenington, 2019), fully confirming the phenomenon.

Interestingly, this in itself has adverse implications for the variation theory. Without cognisance of genic capture, its proponents envisaged a problem dubbed the lek paradox, whereby female choice seemingly would progressively reduce variation and undermine evolution. Consequently, it was assumed that much variation comes from outside the local gene pool: from another population in a very different environment, such that genes that are adaptive in one are maladaptive in the other. However, that's an implausible conjecture. It would be a very unusual gene that has utility in one sub-population of a species but not in another, when they would have to be neighbours for the gene admixture to take place, and, therefore, are hardly likely to have environments sufficiently different to prompt contrasting adaptation. Furthermore, adaptation to changing environment is anyway entrenched in the local gene pool, in that genes (and epigenetic mechanisms) conferring tolerance of any recurring changes are conserved in their anticipation -- these being overwhelmingly the sort of changes locally experienced. Inasmuch as the variation theory was bolstered in being employed to explain the lek paradox, it was undermined when the lek paradox became a paradox no more with the appreciation of genic capture; given genic capture likewise underpins the genome-integrity hypothesis and the related understanding of the function of the sexes as purging mutation.

SUMMARY AND IMPLICATIONS

The present hypothesis that the sexes function to purge deleterious mutation is fully congruent with the gathering profound shift in thinking about the origin and nature of sex: the prospect of the variation theory being overturned in favour of the new hypothesis of maintenance of genome integrity, through repairing DNA. The view of the male being the sex upon which most selection acts is the obvious one that can be integrated into the wider analysis of the function of sex; the only one that would make sense. As would be expected from the sexes evolving after the later stages of meiosis, their function is part of micro-level rather than macro-

level DNA repair mechanism. That the overall function of sex to ensure the integrity of the genome subsumes the function of the male as genetic filter / mutational cleanser (complementing the female reproductive function, which is thereby unencumbered), provides the latter notion with an important additional line of supporting evidence.

It's a striking finding that purging is overwhelmingly or effectively wholly via the male, but this in no way means that no part is played by the female. The male may be the vehicle or conduit of selection, but the female plays an equally crucial, perfectly complementary part in being the *agent* of selection. Males usually are considered the agentic sex, and here indeed this is the case and conspicuously so, in their response to being driven to mutually compete – though note that male competitiveness is here revealed as instrumental rather than primary. Females, however, are agentic in the actual process of selection, in being the active choosers after assessing male genetic quality. The female is far from the passive reproducer. The purging function of the sexes is very much a system across both sexes; not a function of just one sex with the other in its shadow. The picture that emerges of the sexes usurps a simple one of competitive males and reproducing females. It's the more nuanced one of males and females working together to deal with the ongoing mutational threat to future generations inherent in life.

This is foundational, given that with their importance to genome integrity the sexes hardly would be lost or exapted through the course of evolution. On the contrary, they would be evolutionarily very highly conserved. Organismal complexity (the facility to exhibit cultural development not excluded) does not change this, in that it cannot have evolved other than to function to feed back to fine-tune and reinforce its own biological basis (Moxon, 2010). The upshot is that evolved sophistication is ever better manifestation and efficient expression of biological drives: the antithesis of an assumption that what is sex-typical is merely derivative and functionally divergent. Albeit there has to be care in any interpretation tracing far back through evolution, this is not the problem it might appear. Of course, there may be second-order effects that evolve to be no longer apparently sex-typical, and, conversely, there may be the seemingly sex-typical but which arise through convergence, not originating as a male/female manifestation. However, against the continual renewal and honing of what is more directly male/female expression, all else by comparison likely tends to be lost, leaving foundational biology ever shining through.

To very well illustrate: as a mix of these different trajectories, and what, therefore, might be expected thereby to obscure a basis in the male/female divide, are human personality traits. Yet the separation of male and female is so robust in terms of personality that analysis at the level of 10 to 20 traits shows a 90% separation between the sexes (Del Giudice, Booth & Irwing, 2012). That's tantamount to 100% given the error margins in psychology. So at a resolution more refined than the big five, personality variables crystallise out to be not just sex-typical but effectively sex-specific. This extraordinary finding is beyond even what might be anticipated from an understanding of the male/female divide being at the root of sociality and psychology, underscoring its profundity, and allaying any concern that the basis of sex and the sexes as found using simulation or lower animal models somehow would not be applicable to humans. [It is standard in biology to use simple model species and simulation for study to better understand or establish a general principle, being as it's easier to tease out what is going on. It doesn't invalidate the application of findings of a general principle across species. It would be more of an issue to use complex model species, in that there are more likely to be aspects peculiar to the species clouding the principle under investigation.]

The conclusion herein about the sexes has endless implications for the necessarily bottom-up elucidation of human sex differences from what now can be seen to be an underlying and persisting sex *dichotomy*. This facilitates (and augments an already substantial body of) explanation of all aspects of social structure/dynamics, behaviour and cognition, as being in many or most respects sex-specific. It confirms the need for and heralds a revolution in the understanding of human sociality and psychology in terms of radical distinction between the sexes going far beyond mere role – *role* denotes social construction, of course; which notion is now an anachronism in the face of the voluminous evidence of biological basis accruing over several decades.

For so long, male function has not been understood. There has been a failure to recognise that the male contribution to reproduction is as effortful and vital as is that by the female – hardly mere insemination. Male effort has been mis-read and dismissed as mere bidding for individual power: a radically false analysis when it is not appreciated that this is instrumental to what in effect is co-operative differential allocation of reproduction. Whereas the female invests heavily in the wake of conception, the male invests heavily *prior* to conception. Hitherto, the

male has been regarded as the mere foil to the heavy investment in reproduction that renders the female the logjam (the limiting factor) in reproduction – reproduction overall is expandable by increasing the number of females, not by increasing the number of males. In this sense, males are relatively expendable, and hence the default of the female being held in high regard. With greater understanding of the male contribution, it becomes apparent that males collectively make a huge effort in their mutual fierce competition so as to hone what becomes the filtered genetic input to the next generation. The failure to appreciate the male's function appears to be an ultimate instance of the fallacy of guilt by association. The underlying biological reality of the male being the vehicle for the heightened expression and exposure of deleterious mutation (so as to eliminate it through selection) appears to have translated into negative attitudes towards males generically.

With the contrasting respective standard impressions of the sexes revealed to be natural deep-seated prejudices, accounting for our denigrating the male whilst lauding the female, sense can be made of the overall scientific conclusion that instead of the expected misogyny there is philogyny, and in place of anticipated philandry there is misandry (Moxon, 2018). The apotheosis of this truth inversion is contemporary (radical) feminism, which now can be seen as in essence or underpinned by a paleo-conservatism, as it were. A proper understanding of the origin and nature of the sexes exposes much if not all current supposedly progressive wisdom about men and women to be ideological nonsense, reinforced by, if not actually based in much apparent common-sense that in reality is profound anti-male (and pro-female) bias.

All this has a significance for the future of science in that the life sciences are now at risk of contagion from what has infected much of social science -- bugs more pervasive than any already contracted. Feminism and the rest of identity politics has been adopted to the extent that much social science consists of extreme-ideological non- or anti-scientific constructs driving research in a tautological loop of what thereby can appear to have internal consistency yet may have no external validity at all. Biology is viewed a threat in that it can reveal the absence of external validity and bring baseless politicised social science constructs crashing down, so there is and will be far more effort similarly to co-opt biology. In the face of this, proper scientific investigation must be upheld in respect of research into the function of the sexes and its ramifications. Simply ignoring the extreme ideological milieu will not work. Either through an

ideological truth-inversion prism or in the light of science, a choice will have to be made as to which prevails in our culture of two starkly contrasting views: a complete fiction or the full truth about the sexes.

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AUTHOR PROFILE

Steve Moxon is an English independent (non-affiliated) cross-disciplinary researcher/writer of science review papers and books outlining original theory on the biological roots of human sociality, behaviour and psychology, with a special interest in the sexes -- sex difference/dichotomy. Regularly journal-published for the past decade, his topics include dominance hierarchy (and associated reproductive suppression), pair-bonding, partner violence, competitiveness, stress response mechanism, the origin of the sexual divide, and why culture is biology. Throughout is a necessary bottom-up approach, excluding all ideology: an avowed stance against 'PC' ('identity politics'), especially its core of feminism; all being non-, indeed anti-science. Steve also researches/writes re mythologies (ancient and contemporary), these being another window on understanding humanity; and is a songwriter, singer & guitarist. He resides in the Pennine hills north of Sheffield, Yorkshire, where he grew up, feels at home, and can walk or cycle through the stunning countryside of steep-sided wooded valleys and gritstone edges.

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