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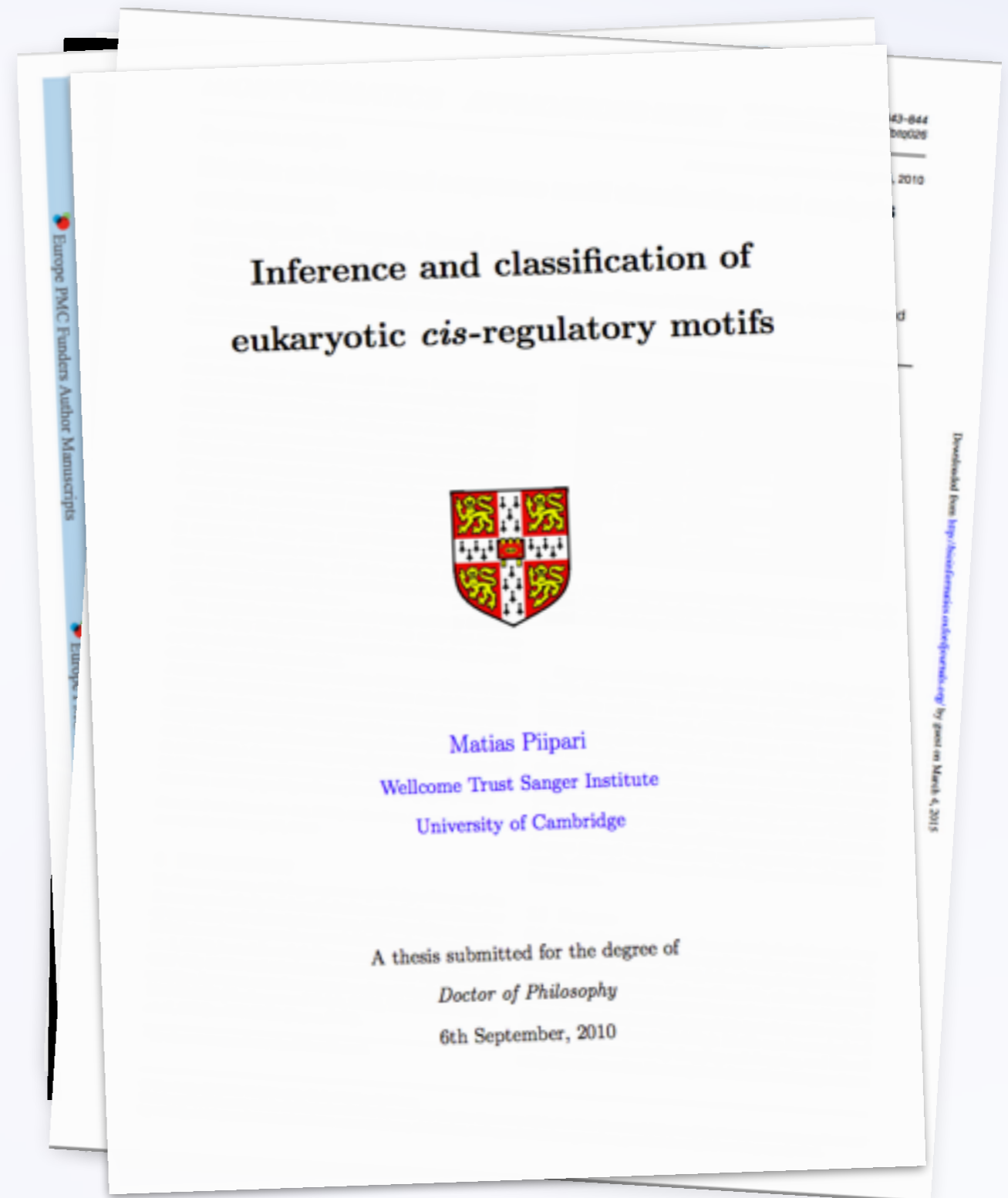
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- Considering the state equ...
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- Results
- Identification of multivale...
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Results

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RNAmotifs: prediction of multivalent RNA motifs that control aleternative splicing

M. Piipari¹, M. Piipari¹, M. Luppi² and A. Griekspoor^{1,2}

¹ Springer, ² Vrije Universiteit Amsterdam

General

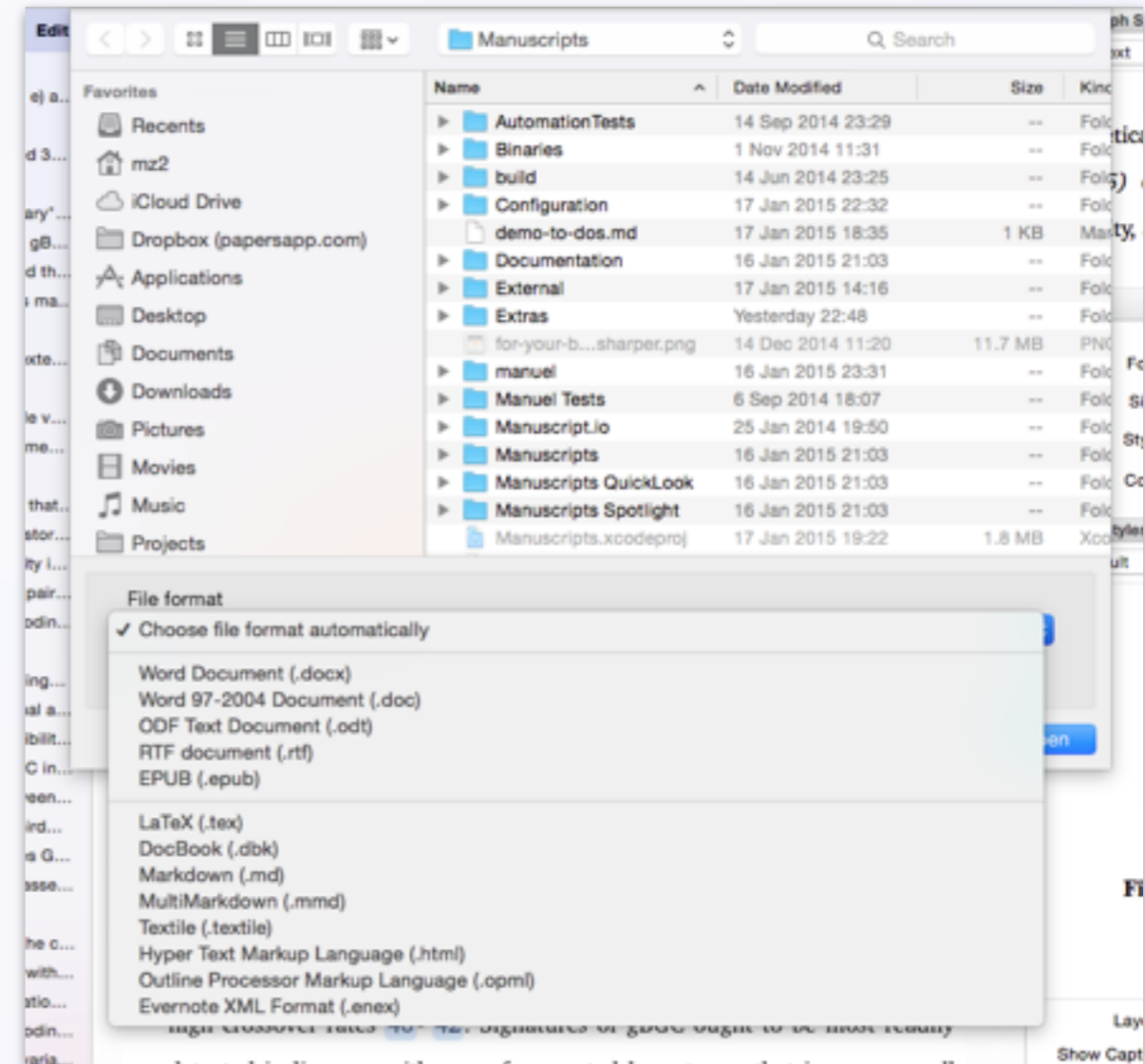
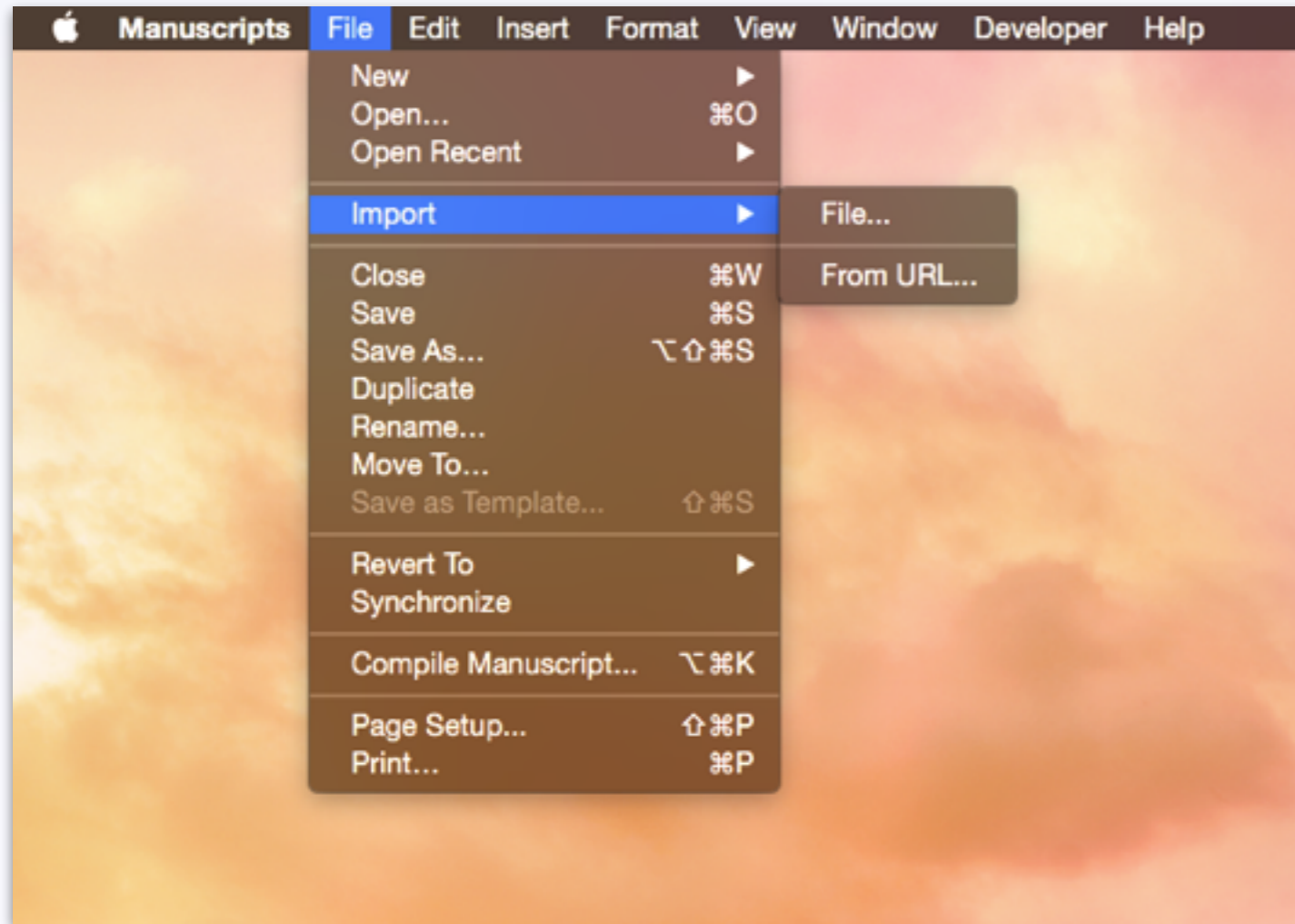
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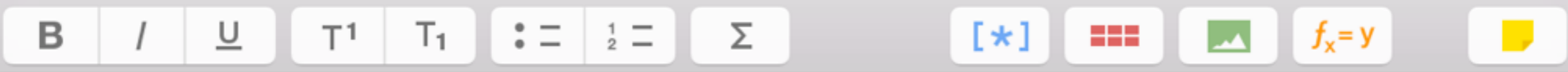
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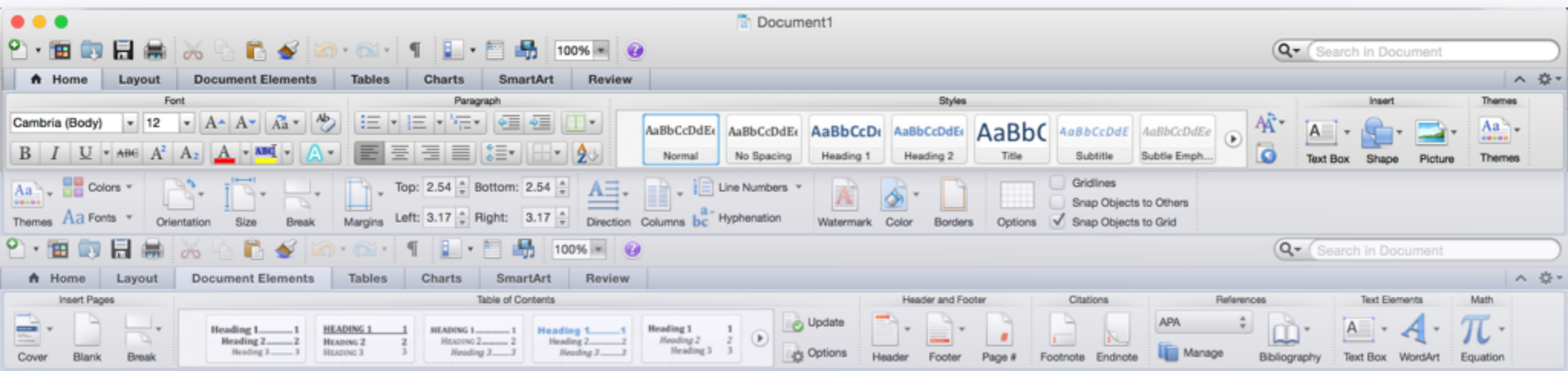




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Tables



Equations



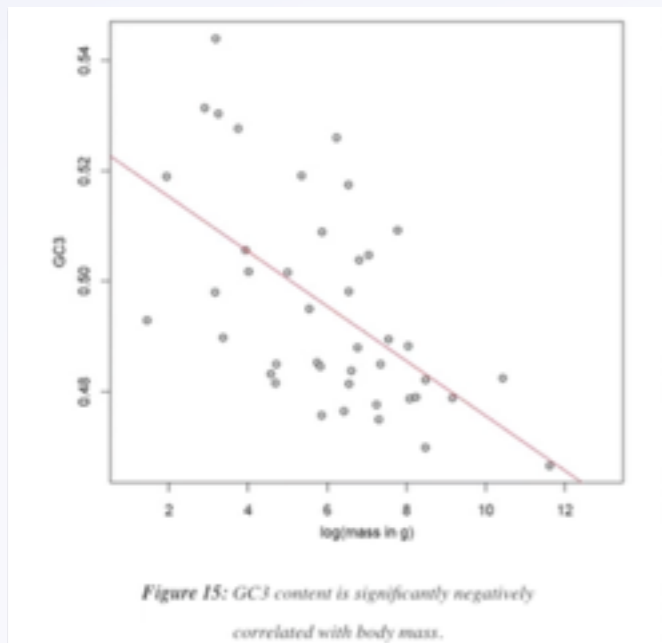


Figure Panels



Tables



Equations





Figure Panels

Mass (g)	GC3
1.2	0.49
3.3	0.50
3.3	0.49
5.9	0.48
2.4	0.52

Column footer 1 Column footer 2

Nucleotide composition at both coding and non-coding regions predicted by body mass

Selective constraint and mutational and neutral forces acting on DNA with each other and modulate to what extent the composition at a given site in species with large effective population sizes, selection against weakly

Tables



Equations





Figure Panels



Tables

$$\mathbf{V}_1 \times \mathbf{V}_2 = \begin{vmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ \frac{\partial X}{\partial u} & \frac{\partial Y}{\partial u} & 0 \\ \frac{\partial X}{\partial v} & \frac{\partial Y}{\partial v} & 0 \end{vmatrix}$$

Equations



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Molecular phenotypes that are causal to complex traits can have low heritability and are expected to have small influence. — Edited

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- 1 Mechanism of the phenotype can alter the stre...
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 - 1 The heritability of a phenotype that is a com...
 - 1 The idea of combining noisy phenotypes to...
- 1 Simple biochemical models predict polygenic...
 - 1 Regardless of the exact definition of heritab...
 - 1 A natural model based on our physical und...
 - 1 Under this view of complex traits, the effect...
- 1 Discussion
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 - 1 These research results caution against takin...
 - 1 Is heritability a useful concept for understan...
 - 1 The generative model of an organism pheno...
 - 1 The explicit models of genotype effect impl...
 - 1 Acknowledgements. I thank Juhan Aru, And...
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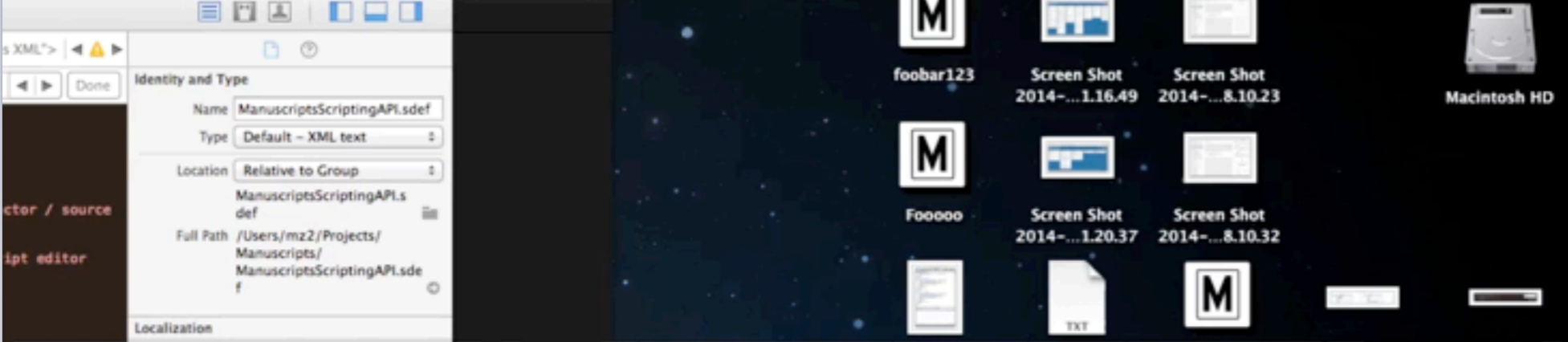
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Even if major genes with larger effects exist, such as rate-limiting steps in pathways (e.g. [48]), many modifiers are predicted.

Discussion

I put forth a statistical and a biological reason why heritability estimates for organism traits can be higher than for their causal molecular phenotypes. From purely numerical considerations, the molecular trait could be defined inappropriately. The genotype signal is present in measurements confounded by stochasticity, timing, location, and assays, but in order for it to have a large relative impact, the phenotype has to be redefined as an integral over the other sources of variation (Klitzing et al. 1980). Any measurement can in principle be used for heritability estimation, thus leaving a choice as to how many different axes of variability to average out, and thereby, how large of a heritability to obtain. A similarly inappropriate definition is positing a standard linear model on a non-Gaussian distribution, which can also reduce the heritability estimate. Biologically, the phenotype itself can be a product of several noisy upstream traits that share some genetic basis. The combination of multiple correlated genetic signals strengthens it, and results in a trait that truly is more heritable than any of its upstream causes. I demonstrated analytically (Supporting Text) that the resulting heritability of a linear combination of traits is the weighted harmonic mean of constituent heritabilities and genetic covariances.

These research results caution against taking heritability estimates of molecular traits at face value, especially for comparisons across multiple studies with different sampling designs and phenotype definitions. They also suggest a tension between integrating signals from genotype and environment over a long time period. Disease risk and many other life-history traits are highly heritable (Manolio et al. 2009), but the estimates can both increase and decrease over time. For example, the heritability of human body-mass index increases from youth to early adulthood, and then decreases again (Nan et al. 2012), suggesting a correlated genotype influence in one period, but sustained environmental effect in another. Any attempt at explaining these phenomena via heritability and genetic basis of molecular phenotypes must be careful in relevant definitions and their interpretation.



[*] Cite



RNAmotifs: prediction of multivalent RNA motifs that control alternative splicing — Edited

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Figure 1 Caption goes here, eventually

Past studies that predicted splicing regulatory motifs from analysis of the differentially regulated exons searched for continuous motifs, which most often identified UGCAUG as the most frequent motif [7-15]. This sequence is recognized by RNA binding protein, fox-1 homologs 1 and 2 (RBFOX1 and RBFOX2), splicing regulators that recognize three nucleotides via the canonical RNA binding surface and an additional four nucleotides via the loops of a quasi-RRM (qRRM) domain (Auweter et al., 2006). However, RBFOX proteins are exceptional in their ability to recognize a long continuous motif, and most other splicing regulators recognize motifs that are only three or four nucleotides long (Auweter et al., 2014; Zhang et al., 2014).

$$J_{\alpha}(x) = \sum_{m=0}^{\infty} \frac{(-1)^m}{m! \Gamma(m + \alpha + 1)} \left(\frac{x}{2}\right)^{2m + \alpha}$$

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 - Co-regulation of alternative exons
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- Discussion
- Conclusions
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 - Definition of multivalent motifs
 - Identification of enriched multivalent...
 - Nucleotide-resolution RNA maps of m...
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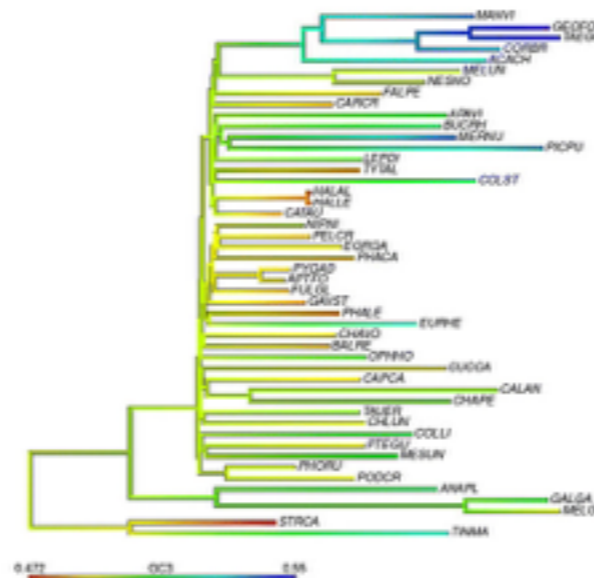
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consider the degree to which different classes of sites are affected, how it corresponds to recombination rate estimates, and whether the impact of gBGC on the base composition of avian genomes is ongoing.

Correlation between GC3 and life history traits is consistent with stronger gBGC in large populations with short generation times

Given the substantial heterogeneity in GC3 content (the proportion of GC at third codon positions) between avian species 33, 47 (Figure 1), we asked whether there is evidence that third codon sites, which should be the least constrained coding positions, might be subject to the influence of recombination-associated gBGC. Species with smaller body mass are expected to have both shorter generation times and larger effective population sizes, increasing both the number of meioses per unit time and the efficacy of gBGC 21, 23. If gBGC is a factor in determining GC, small-bodied species ought then to have elevated GC. This is indeed what we observed, with species with greater body mass exhibiting lower GC3 than species with smaller body mass (Spearman's $\rho = -0.5866$, $P = 6.2e-05$, $n = 42$; see Figure 2). Despite the limited number of species for which data are available, maximum longevity ($\rho = -0.3645$, $P = 0.0616$, $n = 27$) and age of first female sexual maturity ($\rho = -0.5957$, $P = 0.0071$, $n = 19$) showed similar trends, consistent with the possibility that short generation times lead to an increase in GC3 assuming equilibrium has not yet been reached. In the following we only examine body mass, as this maximizes the number of species we can consider.

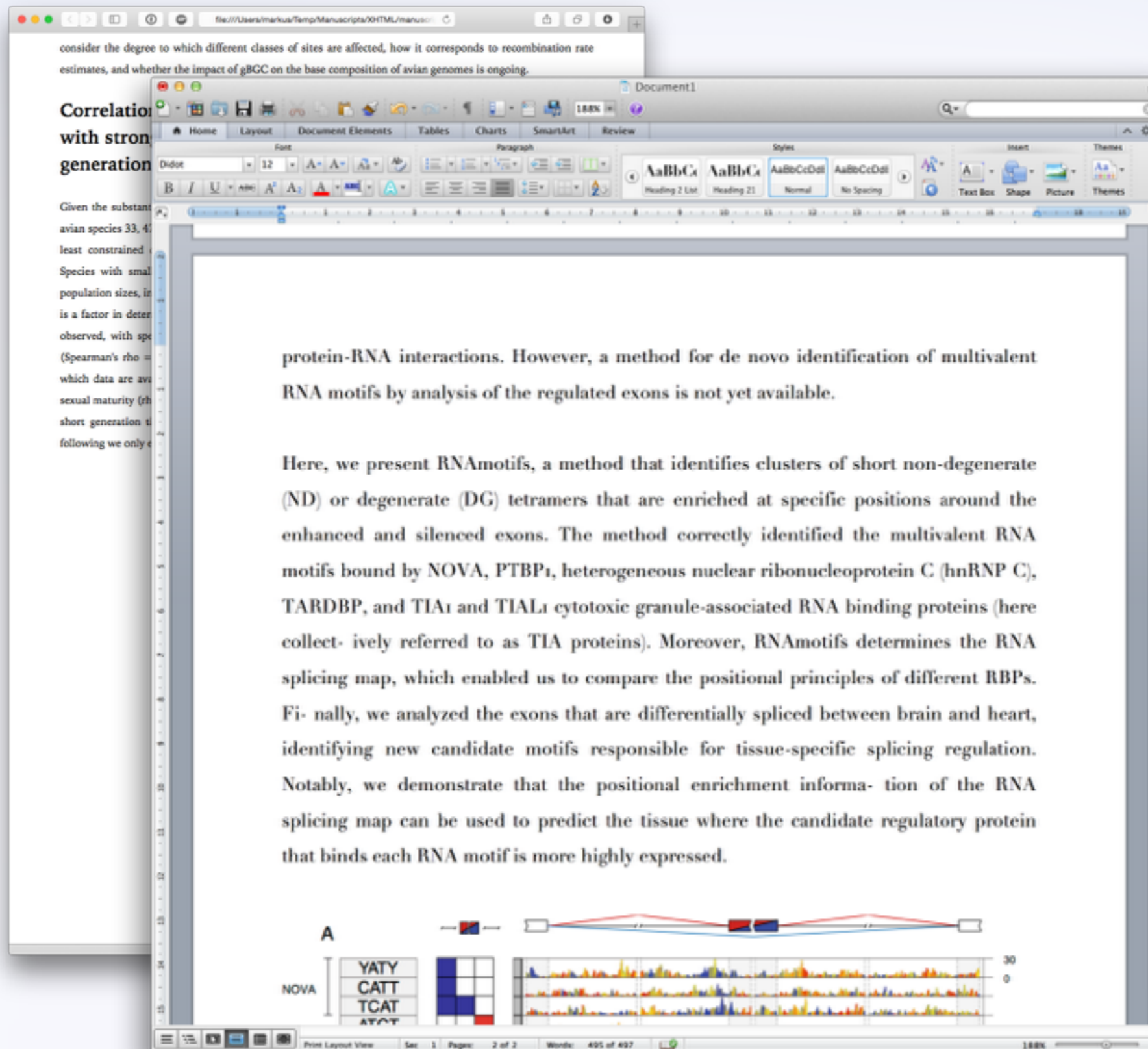


1. GC3 content varies substantially between different avian lineages.

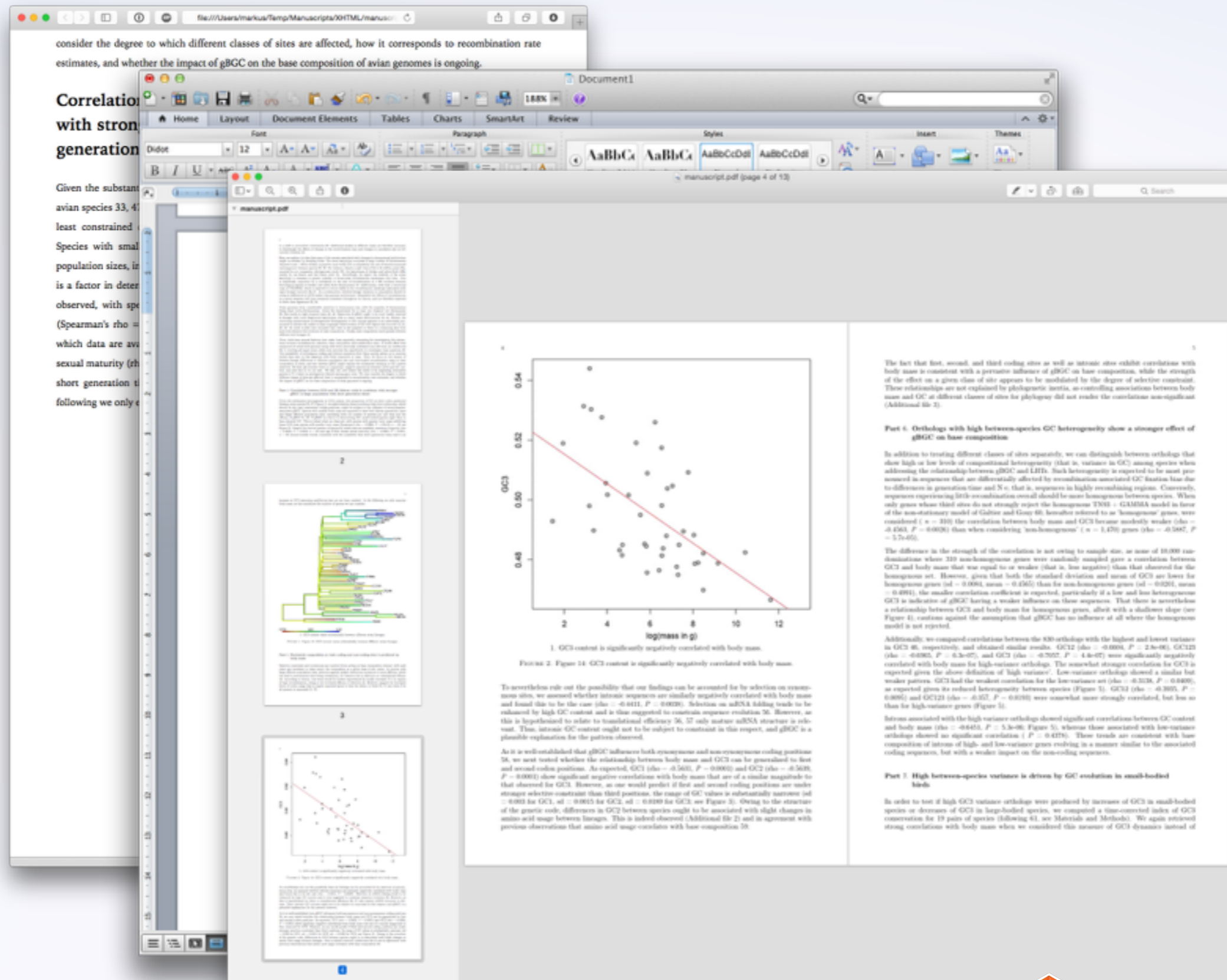
Figure 13: GC3 content varies substantially between different avian lineages.



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iMotifs — Edited

Manuscript

iMotifs: an integrated sequence motif visualization and analysis environment.

Matias Piipari, Thomas A. Down, Harpreet Saini, Anton Enright, Tim J. Hubbard

Abstract

Motivation: Short sequence motifs are commonly used for describing transcription factor binding sites. Motif analysis tools have been recently developed for identifying motifs in DNA sequences, and consequently high-quality binding site predictions for organisms and regulatory factors are therefore important.

iMotifs is a graphical motif analysis and scored motif hits in sequences. It also offers motif inference with the sensitive NestedMICA algorithm, as well as overrepresentation and pairwise motif matching capabilities. All of the analysis functionality is provided without the need to convert between file formats or learn different command line interfaces.

The application includes a bundled and graphically integrated version of the NestedMICA motif inference suite that has no outside dependencies. Problems associated with local deployment of software are therefore avoided.

Availability: iMotifs is licensed with the GNU Lesser General Public License v2.0 (LGPL 2.0). The software and its source is available at <http://wiki.github.com/mz2/imotifs> and can be run on Mac OS X Leopard (Intel/PowerPC). We also provide a cross-platform (Linux, OS X, Windows) LGPL 2.0 licensed library libxms for the Perl, Ruby, R and Objective-C programming languages for input and output of XMS formatted annotated sequence motif set files.

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- Harpreet Saini** (Wellcome Trust Sanger Institute)
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- Joint authorship contribution with previous author:
- Affiliation(s): Wellcome Trust Sanger Institute
- Grant(s): Wellcome Trust (077198/Z/05/Z)
- Summary of contributions: Brief summary of the author's contributions to the manuscript.

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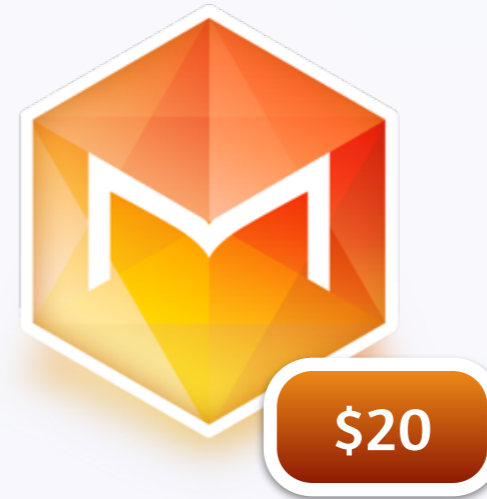


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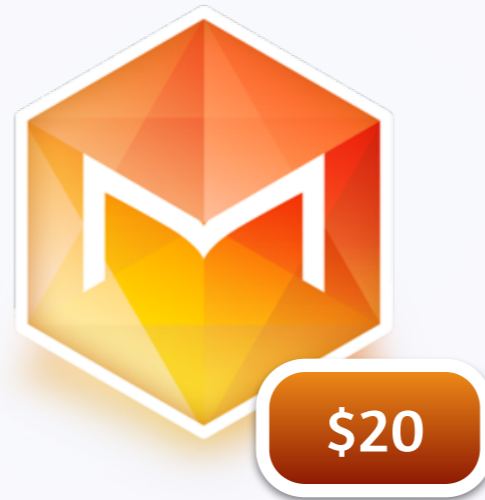


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