Primer

The evolution of haploidy and diploidy

Sarah P. Otto and Aleeza C. Gerstein

Tremendous diversity exists among organisms with respect to their ploidy level, defined as the number of sets of homologous chromosomes per cell. As differences in ploidy represent a potentially major genomic change affecting the evolution of a species, it might be thought that ploidy evolution would be well understood. In fact, our knowledge is fragmentary, and there are several open questions about why ploidy transitions occur when and where they do. Here we provide an overview of diversity in ploidy levels and discuss the large body of theory that has been developed to predict when one ploidy level should predominate over another. We then highlight some of the empirical results that have both helped to clarify our understanding of how evolutionary forces act on ploidy levels and revealed additional levels of complexity.

Ploidy diversity

All sexual organisms, by definition, have life cycles that alternate between two ploidy phases: a reduced state, following meiosis, and a duplicated state, following the union of gametes. For many species, this alternation is between a haploid phase, with one chromosomal set, and a diploid phase, with two sets. Among animals, the haploid phase is generally restricted to unicellular gametes, which do not undergo further mitoses, followed by gamete fusion leading to a diploid phase, which occupies essentially the entire lifespan of the organism.

There are, however, exceptions to this pattern. Most notably, a number of animals consist of haploid males produced parthenogenetically and diploid females produced sexually — 'arrhenotoky', which is characteristic of the monogonont rotifers, pinworms, thrips, and hymenoptera, including bees, wasps, and ants, among others (Normark, 2003). There is even one species of mite that consists entirely of haploid asexual females.

Among plants, mitoses occur in both haploid and diploid phases, with the diploid phase predominating in ferns and seed plants. But polyploidy — having more than two sets of chromosomes — is very common among plants, and evidence is accumulating that all flowering plants have a polyploid history. In some cases, polyploidy is thought to have occurred recently — in the last two centuries, for example, in the cordgrass, *Spartina anglica*, and Welsh groundsel, *Senecio cambrensis*. In many other cases, polyploidization occurred so early in evolution that many of the duplicated genes have diverged substantially or been lost, and chromosomes segregate in the normal fashion of a diploid — as for example, in the ancient polyploidization events in the lineages leading to corn, tomatoes, and *Arabidopsis*.

While the diploid phase predominates among animals, ferns, and seed plants, other multicellular organisms exhibit the entire gamut of possible life cycles (Figure 1), from haplontic, where mitoses are restricted to the haploid phase (Figure 1A), to diplontic, where mitoses are restricted to the diploid phase, as in humans (Figure 1B). Many organisms fall in between these extremes, however, with biphasic (or haploid–diploid) life cycles, where cell divisions and vegetative growth occur in both haploid and diploid phases (Figure 1C). Perhaps the most remarkable life cycle is found in species with an 'isomorphic alternation of generations', where the haploid and diploid phases are morphologically similar, as in the case of the sea lettuce, *Ulva lactuca* (Figure 1C). Isomorphic species demonstrate an important fact about ploidy: individuals of different ploidy levels need not differ substantially at the phenotypic level.

As humans, we are perhaps biased to believe that the diploid phase is evolutionarily favored. There is evidence, however, for evolutionary transitions leading to increased dominance of the haploid phase in several groups, including brown alga, green alga, and several protists. Furthermore, there are species with large and relatively complex haploid phases — for example, the charophytes, known also as stoneworts, a group of green algae closely related to land plants, and some groups of brown and red algae, such as *Mastocarpus* (Figure 1C) — and many other species that are primarily diploid and yet always small, for example, the unicellular diatoms and the *Saccharomyces* budding yeasts.

In short, evolution does not always lead to a decline in the haploid phase and an expansion of the diploid phase, even among multicellular organisms. Among protists, fungi, and algae, there is a great deal of diversity in which ploidy phase dominates. Future phylogenetic work on closely related species that vary in ploidy, such as protists, promises to shed light on when transitions occur between haploid dominance and diploid dominance and the major life history features associated with these transitions. In the next section, we explore how organisms with different ploidy levels exhibit different evolutionary properties and how these properties might, in turn, influence the evolution of ploidy levels.

Evolutionary properties of haploids and diploids

Evolutionary processes differ between haploids and diploids in two key respects: the number of mutations, and the efficiency of selection. There is now a reasonably large body of theory to describe these differences and their implications. Here we provide an overview of the basic evolutionary forces acting in haploids and diploids and how these forces shape ploidy evolution. Depending on the species in question, these forces take on greater or lesser importance, helping to explain why ploidy levels remain so diverse.

The number of mutations

The number of mutations that arise in an individual is directly related to its ploidy level. All else being equal, more mutations arise in diploids than in haploids, simply because they have double the number of mutational targets. Whether or not having more mutations is selectively advantageous depends on the fitness of the organism and the rate at which its environment changes. If an organism is perfectly adapted to a static environment, mutations will only serve to push the individual farther away from its fitness optimum; haploids, with fewer deleterious mutations, might

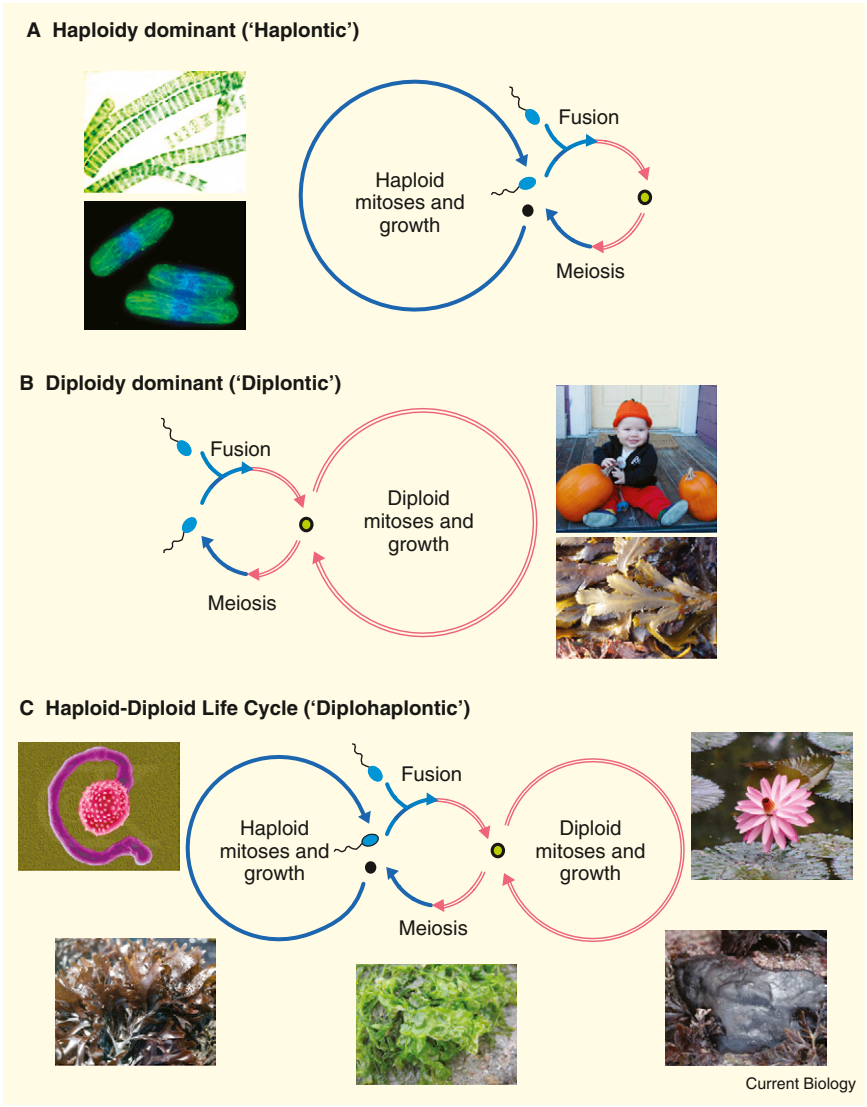

Figure 1. Ploidy diversity.

Sexual life cycles are classified according to the relative timing of gamete fusion and meiosis. (A) Haplontic life cycles undergo meiosis after fusion, with no mitotic divisions in the diploid phase. Examples illustrated: the green alga *Ulothrix*, and the fission yeast, *Schizosaccharomyces* (with permission from Paul Young and Ivan Rupes). (B) Diplontic life cycles undergo fusion after meiosis, with no mitotic divisions in the haploid phase. Examples: humans and the brown alga *Fucus* (http://en.wikipedia.org/wiki/Image:Fucus_serratus2.jpg). (C) Diplohaplontic or biphasic life cycles undergo mitotic divisions in both phases. Examples shown: pollen grain (top left) from a flowering plant (top right), the red alga *Mastocarpus* in the haploid phase (gametophyte, bottom left) and in the diploid phase (sporophyte, bottom right), and the green alga *Ulva*, which is morphologically similar in the haploid and diploid phases (isomorphic alternation of generations, bottom center). Pollen tube image copyright Dennis Kunkel Microscopy, Inc; photos of *Mastocarpus* © Mike D. Guiry/AlgaeBase.

therefore be favored. Conversely, if an organism is not well adapted to its environment, or the environment provides variable challenges, diploids might gain the upper hand by producing more mutations that are potentially advantageous. Here, we say '*might*', because evolution does not just depend on the number of mutations, but also on the fate of these mutations and their selective effects, as discussed next.

The efficacy of selection

Every mutation in haploid individuals, deleterious or beneficial, is immediately expressed. In contrast, mutations first appear among diploids in heterozygous form. Consequently, selection is better able to 'see' the fitness effects of mutations in haploids than in diploids. As a result, deleterious mutations are more efficiently eliminated and reach lower equilibrium frequencies in haploids than in diploids. In mathematical terms, if we let $\hat{q}$ describe the equilibrium frequency of deleterious mutations, which occur at rate μ and reduce fitness by s in haploids and by hs in heterozygous diploids, then the equilibrium frequency of deleterious mutations can be shown to be lower in haploids ($\hat{q} = \mu/s$) than in diploids ($\hat{q} = \mu/(hs)$), by the factor h, which measures the dominance of the mutation. Similarly, beneficial mutations more easily spread in haploid populations than in diploid populations. Indeed, the time that it takes for a beneficial mutation to rise from a single copy to complete fixation is roughly twice as long in diploids (Figure 2).

Furthermore, beneficial mutations are much more likely to be lost by chance after they first appear in diploid populations, simply because masking in diploids causes the fitness benefits of mutations to be partially lost. Indeed, the probability that a favorable mutation persists within a population, rather than being lost by chance, is higher in haploids (~2 s) than in diploids (~2 hs), by a factor, 1/h (assuming that the mutation arises in a single individual and that the number of offspring per parent is approximately Poisson distributed).

According to these ideas, diploid organisms should be more fit when evolutionary change is limited by mutation, whereas haploid organisms should be more fit when evolutionary change is limited by selection. What the optimal ploidy level is, and how ploidy levels should evolve, must then depend on the balance between these factors. In the following, we focus in on particular scenarios to better understand this balance.

Scenario 1: deleterious mutations

When mutations are deleterious, it is always costly to have more mutations, and haploids have the highest equilibrium fitness. Accounting for the frequency of mutant individuals — $\hat{q}$ in haploids and roughly $2(1 - \hat{q})\hat{q} \sim 2\hat{q}$ in diploids — and the fitness effects of mutations, deleterious mutations reduce mean fitness by an amount μ (= $\hat{q} \times s$) in haploid populations and by roughly 2μ (= $2\hat{q} \times hs$) in diploid populations.

Thus, at equilibrium, diploid populations suffer twice the number of selective deaths due to mutation as do haploid populations. This result does not depend on the efficiency of selection, because the frequency of deleterious mutations at equilibrium is inversely proportional to the strength of selection — weaker selection just leads to more mutations segregating within a population, and the strength of selection, *s*, cancels out from the mean fitness of the population at equilibrium.

According to this scenario, haploidy is the optimal state at equilibrium because haploids suffer from the lowest load of inherited mutations. Does this mean that evolution always favors transitions to haploidy? The answer is 'no' for an interesting reason. Imagine a predominantly haploid population in which a gene variant appears that causes meiosis to be delayed; we'll call this variant a 'modifier' allele. Individuals carrying this modifier spend more time in the diploid phase, within which deleterious mutations are masked by alleles on the homologous chromosome. Thus, this modifier can spread, not because it is ultimately good for the species (it isn't), but because the modifier benefits its individual carriers by reducing the chance that they'll die from the deleterious alleles in their genome. Overall, theoretical studies have shown that an expansion of the diploid phase is favored as long as deleterious mutations are masked (partially recessive), and as long as there is enough sex and recombination in the population to ensure that the modifier does not get loaded down by its linkage to deleterious alleles.

Somatic mutations also favor the expansion of the diploid phase. Mutations that would give rise to uncontrolled cell growth and cancer in haploids, for example, can be masked by the non-mutated allele on the homologous chromosome in diploids. As a specific example, retinoblastoma (cancer of the retina) is rare among humans with two functional copies of the *Rb* gene but common in individuals with only one functional copy. Indeed, there is a tendency for organisms that are larger and that contain more specialized cell types to be diploid rather than haploid. In this case, expansion of the diploid phase is favored because diploids are more likely to survive the onslaught of mutations that occur during development and hence more likely to pass on modifiers promoting the diploid phase to the next generation, despite the fact that diploids have higher equilibrium loads of inherited mutations.

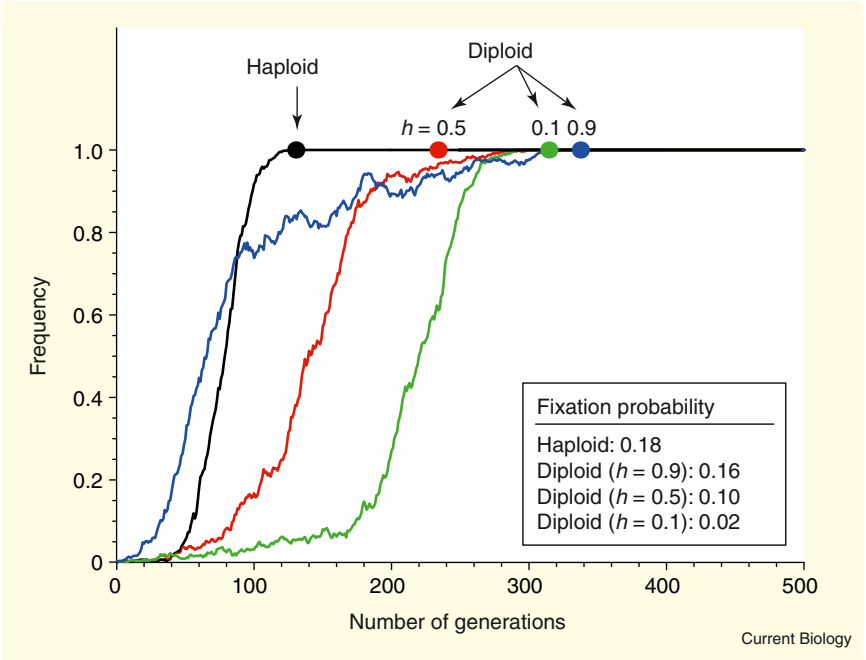

Figure 2. Selection is more efficient in haploids.

The figure illustrates the spread of a beneficial allele that increases fitness by 10% ($s = 0.1$) and that arises in a single copy within a population of size 2000 haploids or 1000 diploids (each carrying two alleles). On average, the allele fixes faster in haploid populations (black dot at 130 generations) than in diploid populations (dots at 234, 314, and 337 generations with $h = 0.5$, 0.1, and 0.9, respectively). The dots give the average fixation time based on a diffusion analysis, and the curves illustrate one sample trajectory. In addition, beneficial alleles are more likely to persist rather than being lost by chance in haploid populations (inset table).

Scenario 2: beneficial mutations

With double the number of mutational targets, beneficial mutations should arise twice as often in diploids than in haploids, all else being equal. But having more mutations doesn't matter if these mutations are masked and lost soon after they first appear. Because the risk of loss is more than doubled in diploids than in haploids when beneficial mutations are partially recessive ($h < ½$), we expect haploids to evolve faster in this case. Even when beneficial mutations are partially dominant, however, the fact that they spread at a lower rate in diploids than in haploids (Figure 2) can give haploid populations the upper hand at adapting to novel environments.

In asexual species, theoretical work addressing the rate of adaptation has demonstrated that diploids evolve faster than haploids if beneficial mutations are sufficiently dominant *and* if the appearance of beneficial mutations is a rate-limiting step (for example, at small populations sizes). Otherwise, if mutations are abundant (for example, in large populations), the spread to fixation of these mutations is predicted to be the primary rate-limiting step, and haploids should adapt faster.

Scenario 3: genetic potential

Under the right circumstances, diploid organisms can benefit from having a greater potential for genetic variation. Because deleterious recessive mutations reach higher frequencies in diploids than in haploids, these mutations can become a ready source of genetic variation if the environment were to change and the mutations were to become beneficial. Whether this scenario is an important factor favoring diploidy remains to be assessed. In particular, if mutations that were recessive when they were deleterious remain recessive when they are beneficial, they may be only weakly selected in the novel environment.

Diploid genomes also harbour the potential to utilize different variants of a gene, making it possible for diploids

to gain a fitness advantage whenever there is heterozygote advantage. In other words, diploids can take advantage of divergence in function between the two allelic copies carried by an individual. As a particular example, consider a gene that confers resistance of hosts to parasites by allowing the host to recognize a foreign antigen and mount an immune reaction. At these recognition loci, carrying two alleles can improve the chances that a diploid host will be able to recognize a parasite and resist infection. Thus, diploids benefit whenever carrying two allele copies provides a greater genetic potential to carry out multiple functions. Of course, this evolutionary force would not just favor diploidy, but would also favor gene duplications.

The converse possibility also exists, if carrying multiple variants is disadvantageous and reduces the fitness of diploids relative to haploids. Parasites that are diploid, for example, run the risk of expressing two antigen alleles, doubling the chance that they will be recognized and cleared. The implication is that haploid life cycles should be favored in parasites (and parasitism should be easier to evolve in haploids). This prediction is broadly consistent with patterns among protists, where parasitic protists (like malaria-causing *Plasmodium* and the sexually transmitted disease-causing *Trichomonas vaginalis*) are four times more likely to be haploid than are non-parasitic protists.

Non-genetic scenarios

In the scenarios considered above, we focused on genetic differences between haploids and diploids. But changes in ploidy can also have immediate phenotypic effects. As one particular example, haploid cells are often smaller than diploid cells, and by nature of cell geometry, haploid cells consequently have a larger surface area to volume ratio than diploid cells. It has been suggested that haploids should consequently be better able to deal with nutrient limitation, because they can take in nutrients proportionally faster than can diploids. Diploid cells, in contrast, might be better able to tolerate toxic environments, because of the smaller surface area in contact with the external environment relative to their volume. These predictions are most relevant for single-celled organisms, as body size in multicellular species need not be directly affected by ploidy.

Testing evolutionary hypotheses

Empirical evidence is needed to indicate how the various factors discussed above interplay to favor haploid versus diploid life cycles. Fortunately, there are a growing number of studies that have experimentally manipulated ploidy levels to assess their evolutionary impact, especially using the budding yeast, *Saccharomyces cerevisiae*. Highlights of this research include:

- Haploids are less fit than diploids following exposure to mutagens, consistent with the ability of diploids to mask mutations (Mable and Otto, 2001).
- Haploids adapt relatively faster than diploids to environments that require partially recessive adaptive mutations but not in environments that require dominant adaptive mutations (Anderson *et al.,* 2004).
- Haploids adapt relatively faster than diploids when populations are larger than when they are smaller (Zeyl *et al.,* 2003). This result is consistent with the prediction that selection is limiting in large populations and mutations are limiting in small populations.
- Haploids are more fit than diploids under some conditions of nutrient limitation, but not under others. Further work is needed to determine the exact environmental conditions that favor small haploid cells versus large diploid cells.

A large body of ploidy research has also looked at those algal groups that contain biphasic life cycles, especially species of brown (*Phaeophyta*), green (*Chlorophyta*) and red (*Rhodophyta*) algae. For example, one comparative study found evidence for an ecological role of ploidy variation: the haploid phase in brown algae tends to be physically reduced perhaps because this increases the chance that they release gametes into a boundary layer where they are more likely to encounter other gametes, whereas a large diploid phase allows for greater spore dispersal (Bell, 1997). Studies in isomorphic taxa have also been useful in highlighting the particular demographic, physiological, and ecological features of a species that cause one phase to predominate over the other (Thornber, 2006).

Conclusion

It is remarkable that one of the most fundamental features of an organism — its ploidy level — is so variable among taxa, with life cycles running the entire gamut from complete haploid dominance to complete diploid dominance. Theoretical studies have clarified many important genetic advantages to haploidy (for example, lower mutation load, more rapid spread of beneficial alleles) and to diploidy (for example, protection from somatic mutation, heterozygote advantage). More and more, these advantages are being experimentally tested and validated. A major open question, however, is to what extent are the genetic effects of haploidy and diploidy important in nature? Are these genetic effects often trumped by ecological differences between individuals in the haploid and diploid phase? Experiments exploring fitness and adaptation of haploids and diploids across a range of environments promise to shed some light on the relative importance of genetics and the environment in shaping the patterns of life cycle diversity surrounding us.

Further reading

Anderson, J.B., Sirjusingh, C., and Ricker, N. (2004). Haploidy, diploidy and evolution of antifungal drug resistance in *Saccharomyces cerevisiae*. Genetics *168*, 1915–1923.

Bell, G. (1994). The comparative biology of the alternation of generations. Lectures Math. Life Sci. *25*, 1–26.

Bell, G. (1997). The evolution of the life cycle of brown seaweeds. Biol. J. Linn. Soc. *60*, 21–38.

Gerstein, A.C., and Otto, S.P. (2009). The causes of evolution in the era of genomics. J. Hered., in press.

Goldstein, D.B. (1992). Heterozygote advantage and the evolution of a dominant diploid phase. Genetics *132*, 1195–1198

Mable, B.K., and Otto, S.P. (1998). The evolution of life cycles with haploid and diploid phases. BioEssays *20*, 453–462

Mable, B., and Otto, S.P. (2001). Masking and purging mutations following EMS treatment in haploid, diploid and tetraploid yeast (*Saccharomyces cerevisiae*). Genetic. Res. *77*, 9–26.

Normark, B.B. (2003). Evolution of alternative genetic systems in insects. Annu. Rev. Entomol. *48*, 397–423.

Nuismer, S., and Otto, S.P. (2004). Host-parasite interactions and the evolution of ploidy. Proc. Natl. Acad. Sci. USA *101*, 11036–11039.

Orr, H.A. (1995). Somatic mutation favors the evolution of diploidy. Genetics *139*, 1441–1447.

Thornber, C.S. (2006). Functional properties of the isomorphic biphasic algal life cycle. Integr. Comp. Biol. *46*, 605–614.

Zeyl, C., Vanderford, T., and Carter, M. (2003). An evolutionary advantage of haploidy in large yeast populations. Science *299*, 555–558.

Department of Zoology, University of British Columbia, Vancouver BC, V6T 1Z4 Canada.
E-mail: otto@zoology.ubc.ca