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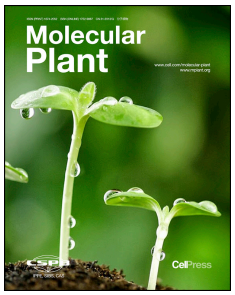

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Tension and resolution: Dynamic, evolving populations of organelle genomes within plant cells

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Short summary

Complex life is powered by mitochondria and plastids, which form dynamic, evolving populations within plant cells. Here we review the coupled physical and genetic behaviour of these vital populations, and hypothesise that an evolutionary tension can account for several dramatic differences between plant organelles and those in other kingdoms.

Abstract

Mitochondria and plastids form dynamic, evolving populations physically embedded in the fluctuating environment of the plant cell. Their evolutionary heritage has shaped how the cell controls the genetic structure and the physical behaviour of its organelle populations. While the specific genes involved in these processes are gradually being revealed, the governing principles underlying this controlled behaviour remain poorly understood. As the genetic and physical dynamics of these organelles are central to bioenergetic performance and plant physiology, this challenges both fundamental biology and strategies to engineer better-performing plants. This article will review current knowledge of the physical and genetic behaviour of mitochondria and chloroplasts in plant cells. An overarching hypothesis is proposed, whereby organelles face a tension between genetic robustness and individual control and responsiveness, and different species resolve this tension in different ways. As plants are immobile and therefore subject to fluctuating environments, their organelles are proposed to favour individual responsiveness, sacrificing genetic robustness. Several notable features of plant organelle dynamics including mtDNA recombination and plastid/mitochondrial differences may be explained by this hypothesis. Finally, the article highlights how tools from quantitative and systems biology can help shed light on the plethora of open questions in this field.

Introduction

Bioenergetic organelles – mitochondria and chloroplasts – power complex life. Chloroplasts are responsible for photosynthesis, producing ATP in the light, fixing 120Pg (1Pg (petagram) = 10^{12} kg) of carbon each year [1], and providing the 2.46Pg per year of grain yields that feed the human world [2]. Mitochondria are responsible for plant respiration, releasing 60Pg of carbon per year [1] and producing ATP across plant tissues and environments. Together, these plant organelles are the fundamental biological actors in the biosphere's energy and carbon budgets.

Both mitochondria and plastids (the broader class of organelle of which chloroplasts are one differentiated type) have a rich and fascinating evolutionary heritage. Both are descended from free-living precursors. Absorbed by ancestral 'host' cells through endosymbiotic events [3, 4], these precursors retained aspects of their identity in what became a symbiotic relationship. Modern organelles retain genomes – mtDNA (mitochondrial DNA) and ptDNA (plastid DNA, contained in chloroplasts and in other plastid forms). Throughout evolutionary history, as endosymbionts have become organelles, the (originally full) complements of genes contained within these genomes

have been dramatically reduced [5, 6, 7, 8, 9] in an ongoing coevolutionary game that has defined the genesis and evolution of eukaryotic life [10, 11, 12, 8, 9].

Most organelle genes have either been transferred to the nucleus or lost completely. Generally, transfer to the nucleus sequesters these genes in a safer environment at the cost of reducing individual organellar control of gene expression [7, 13, 9]. The pressures leading to the loss or retention of specific organelle genes have been debated for decades [14, 15, 16, 17, 8, 18], supported by ongoing genetic studies elucidating the evolutionary dynamics of plant mtDNA [19, 20] and ptDNA [21, 22, 23, 24]. Striking experiments in tobacco have demonstrated that transfer of genes from the plastid to the nucleus is frequent enough to be explored over experimental timescales [25]. Large-scale genomic data and statistical modelling continue to shed quantitative light on these open questions [26, 18, 23, 27], exploiting the increasing volume of organelle genome data, with 235 mitochondrial and 2716 chloroplast/plastid genomes labelled as ‘plants’ on NCBI at the time of writing [28].

Today, mitochondria and plastids exist in dynamic populations in plant and algal cells. The size of these cellular populations vary. Some algae (for example, *Chlamydomonas reinhardtii*) have only a single chloroplast per cell [29]; some plant cells contain many dozen tightly-packed chloroplasts [30]. Cellular populations of mitochondria also vary in number from single (for example, in the red alga *Cyanidioschyzon merolae* [31]) to the hundreds or thousands. Plastids in green tissues have usually differentiated into chloroplasts; in, for example, root tissue, they remain in undifferentiated forms [32, 33]. These organelles contain the reduced genomes that reflect their evolutionary heritage, maintained in dynamic populations inside cells [6, 34, 35]. In plant cells, there are often fewer mtDNA molecules than mitochondria, and more ptDNA molecules than plastids [36, 37, 38]. The sets of genes retained by these organelles are of central importance to bioenergetics and eukaryotic life, dictating organelle responses to changing conditions [13, 39]. As a result, the dynamics of these cellular populations have profound implications from the systematic study of plant evolution [40] to hybrid crop breeding [41, 42, 43, 44] and biotechnology [45].

These cellular populations of molecules are embedded in physical organelles, and their population structure and dynamics is tied to the behaviour of their compartments. Recent and ongoing developments of fluorescent reporter lines and microscopy tools and techniques have revealed the intricacy and dynamism of organelles within cells [46, 47]. Elegant work over the last two decades [48, 49, 50, 51, 37] has shed light on the rich dynamics of mitochondria in plant cells and the notable differences from the more-studied mammalian world. Plastids, particularly chloroplasts, exhibit highly dynamic physical responses to their environment, particularly light conditions [52, 53, 54]. The cell invests considerable resource in maintaining the motion and cellular structure of organelle populations, some reasons for which remain poorly understood [55].

Perturbations to the genetic and physical dynamics of organelles have dramatic consequences forplants, including compromising growth and photosynthesis and inducing male sterility. Despite this importance, multiscale questions remain open in our understanding of the control and maintenance of organelle populations. Systems biology and modelling approaches offer the opportunity to build theoretical foundations with which to understand these phenomena. Given the complex co-evolutionary history of organelles and plant cells, the paradigm of evolutionary systems biology (encompassing, amongst other topics, the evolution of regulatory systems and genotype-phenotype maps [56, 57]) is of particular pertinence. This review will attempt to synthesise existing knowledge of the

complex genetic and physical behaviour of plant organelles through the lens of evolutionary systems biology, highlighting where quantitative and interdisciplinary approaches can make progress understanding the evolved mechanisms governing these ubiquitous and vital systems.

Organelle genomes in plant cells – general principles

Ref. [34], in reviewing the similarities and differences between mitochondria and chloroplasts, cautions that seeking single explanations for their similarities may be an 'oversimplistic trap'. However, keeping this risk in mind, it is tempting to consider what may constitute general pressures on these organelles.

First, the reduced genomes of both modern mitochondria and plastids encode subsets of the products necessary for organelle function, including subunits of the organelles' electron transport chains and ribosomes, tRNAs and rRNAs (Fig. 1). The remaining genes necessary for organelle function are encoded by the nucleus. Communication and co-operation between organelles and the nucleus is therefore vital for bioenergetic functionality [8].

The genetic integrity of organelle genomes must be retained in the face of stochastic mutagenic events [58]. Some studies hypothesise that redox imbalance – a difference between pro-oxidant production and anti-oxidant defences – is an important source of DNA damage [59, 60]. As the bioenergetic activity of mitochondria and chloroplasts involves highly dynamic redox processes, organelle genomes may be particularly subject to mutational damage. This link is subject to some controversy: experiments manipulating the severity of oxidative damage have not induced dramatic changes in mitochondrial mutation rates [61], and detailed analysis of mtDNA mutational profiles during ageing suggest a dominant role for replicative errors or other mutagenic events over oxidative damage [62]. Regardless of the weighting of these different influences, the comparative lack of protective DNA packaging, and frequent replication of organelle genomes, makes organelle DNA highly susceptible to potential mutation. Muller's ratchet – the ongoing buildup of deleterious mutation [63] – must be avoided in organelle inheritance.

Cellular noise and organelle populations

In addition to mutational damage, plant organelles also face physical and environmental challenges. These reduced genomes are physically embedded in their host organelles, in a noisy cellular world [66, 67]. Stochasticity due to low copy numbers and diffusive dynamics dominates many cellular processes, and cells' ability to suppress the resulting fluctuations is subject to fundamental theoretical limits [68]. Cellular populations of organelles must be controlled to fulfil cellular energy needs against the background of this noisy world [69, 70, 71, 72, 73, 74].

Figure 1: Organelle genomes in *Arabidopsis*. (A) Circular mapping of mtDNA (NCBI NC 037304), encoding some (not all) subunits of Complexes I-IV, ATP synthase, the mitochondrial ribosome, tRNAs and rRNAs. The genome is much larger than the familiar 16kb mammalian mtDNA, with large non-coding regions. (B) Circular mapping of ptDNA (NCBI KX551970), encoding some (not all) subunits of photosystem complexes, electron transport chain proteins, the plastid ribosome, tRNAs and rRNAs. The genome is divided into large and small single copy regions (LSC and SSC) separated by inverted repeat regions IRA and IRB [64]. Figures adapted from output of OGDRAW [65].

An important and general source of genetic and physical noise in organelle dynamics is the partitioning of organelles when cells divide. The variability associated with organelle partitioning at cell divisions has been an active area of research for decades [75]. Early results on algae plastids suggested that partitioning was rather stochastic and the consequent variability was mitigated by subsequent control of organelle replication [76]. Recent results have showed tighter-than-random control of the partitioning of some cellular components [70], with results on mitochondria compatible with stochastic models involving a binomial partitioning picture and subsequent replication control [72, 77]. Further, organelles are inherited uniparentally in most circumstances [12], requiring a physical mechanism to degrade or otherwise remove organelles from one parent between generations [78, 79].

Intracellular dynamics provide more noisy influences on organelle genome populations. Organelle genomes replicate, degrade, and may recombine within cells. These processes take place in the noisy physical environment of the cell and so contribute to stochasticity in organelle populations within and between cells. A common consideration here is the *heteroplasmy* of a cell: the proportion of mutated or foreign organelle genomes in the cellular population. Heteroplasmy may arise from mutation, inheritance of more than one organelle genotype, or synthetic introduction of foreign organelle DNA into a cell.

Experimental observation of single-cell organelle genome populations over time is challenging. Pioneering work in single-celled organisms yielded results including the rates of genetic drift and recombination shaping heteroplasmic cellular populations of mitochondria in yeast [80] and the dynamics resulting from controlled chloroplast replication in algae [76]. Several experimental studies, referenced in sectionsbelow, have explored the genetic structure of organelle populations in plant cells at different developmental times, but time-course experiments on organelle genomes dynamics in plants remain limited. The dynamic study of heteroplasmic organelle populations remains more established in the animal kingdom, where mtDNA and heteroplasmy dynamics have been studied in mouse and other animal models, and human cells (reviewed in Ref. [81]).

Due to these experimental challenge, a range of mathematical and modelling studies have explored the behaviour and principles shaping organelle genome populations (recently reviewed in Ref. [82]).

These models usually picture organelle genome replication and degradation as random processes occuring with characteristic rates. A central question addressed by these models is whether random genetic drift explains the dynamics of heteroplasmic populations, or if there is evidence of differential selection on different organelle genotypes. To this end, classical results from population genetics [83] have been leveraged to predict the distribution of organelle heteroplasmy in cells under neutral drift [84]. This work is complemented and extended by stochastic modelling approaches considering well-mixed cellular populations of discrete organelles [71, 77, 85, 86, 87]. These approaches have, for example, helped identify tissue-specific selection shaping heteroplasmy over time [88], and characterised the increase in cell-to-cell heteroplasmy variance over time during development and ageing [77, 89]. This dynamic increase in variance has been shown to be independent of cellular attempts to control organelle content [71]. Modelling work has also revealed the quantitative capacity and limits of such cellular control [90].

Other modelling approaches impose some spatial structure within the model cell to explore the joint physical and genetic behaviour of mitochondrial genomes [91, 92, 93, 94]. These

studies consider the impact of mitochondrial fission and fusion on the genetic makeup of cellular populations. Insights from this work include that slower fission-fusion dynamics lead to faster increases in heteroplasmy variance [91, 92], and that selective mitochondrial fusion can act to diminish cellular heteroplasmy [93, 82]. The propagation of mutation load in development to pronounced organelle heterogeneity in developed organisms has also been quantitatively highlighted [94].

Much of this modelling work has focussed on the animal kingdom. While many of the principles may be expected to hold in plant cells, we will see below that several unique features of organelle populations mean that more theoretical study is needed in the plant kingdom. Stochastic modelling approaches specifically in plant systems include classical work on mtDNA recombination in plants [95, 96], which has revealed the influence of multiscale selection on the complex mtDNA populations of plant cells, and the dynamics and reversibility of mtDNA rearrangements due to recombination, described in more detail below.

An evolutionary tension underlying organelle genome evolution

In addition to these sources of cellular noise, plants are immobile and must survive in fluctuating environments. Taken together, plant cells thus face the challenge of *controlling the structure and function of organelle populations in the face of mutagens, physical noise, and fluctuating environments*.

How does this challenge manifest in the structure and dynamics of organelle populations? The CoRR (colocation for redox regulation of gene expression) hypothesis is an elegant theory that phrases the observed evolutionary dynamics of organelles in the language of this cellular control [97, 13]. CoRR suggests that *expression of genes for protein subunits of energy-transducing enzymes must respond to physical environmental change by means of a direct and unconditional regulatory control – control exerted by change in the redox state of the corresponding gene product* [13]. Here, genes are evolutionarily retained in organelle genomes because they allow organelles to directly regulate expression of key components of energetic pathways. Competing theories have questioned the mechanism by which a subset of organelle genes can exert control on the function of bioenergetic machinery, given that nuclear genes are invariably also required [60]. One possible answer is suggested by recent work showing that genes encoding more central subunits of the electron transport chain are more likely to be retained in mitochondria [18]. This observation suggests a picture where genes that ‘set the pace’ for complex assembly are retained by organelles [98]. For example, consider the case where an environmental challenge means that an individual mitochondrion requires a new copy of Complex I. If that mitochondrion can intrinsically express ‘core’ Complex I genes, these can nucleate assembly of the required new complex *in situ* using nuclear-expressed ‘periphery’ subunits imported from the cytosol. If mitochondria cannot intrinsically express genes, all core and periphery subunits must be expressed in the nucleus. Then, the original mitochondrion may obtain a new complex, but so may all other mitochondria in the cell, challenging regulation at the level of the individual organelle.

An alternative redox-based hypothesis has been presented [60] where organelle DNA itself acts as a long-term redox sensor. Damage to DNA manifests as altered activity of the enzymes that the DNA encodes, which is sensed by the nucleus as a readout of redox poise. Other hypotheses for the retention of organelle genes include the difficulty of importing hydrophobic gene products to the organelle from the nucleus [16, 99], genetic code incompatibility, and others (compared in [18]). Importantly, many of these hypotheses

are neither incompatible nor exclusive: Bayesian model selection harnessing large-scale genomic data reveals support for several mechanisms acting together (hydrophobic, energetically central products of genes with high GC content are retained), partly explaining the ongoing debate in the field [18].

CoRR, redox sensing, and many other hypotheses suggest that retaining genes in organelle DNA enhances the ability of organelles to efficiently respond as individuals to fluctuating demands and/or conditions. If this general principle is true, a universal tension underlies organelle evolution (Fig. 2). This tension is between avoiding mutational damage and retaining organelle genes for regulatory and/or biophysical reasons. The diverse modern-day populations of organelle genomes in cells may then be viewed as a spectrum of resolutions to this consistent evolutionary tension. That different organisms have adopted different positions on this tradeoff – visualised as a Pareto front in Fig. 2C – may reflect the diversity of environmental and pressures across life. For example, mirroring dramatic gene loss in other parasitic taxa, parasitic plants like mistletoe have lost many mitochondrial genes [100] (indeed losing bioenergetic machinery completely rather than transferring to the nucleus [101]), suggesting a balancing towards genetic robustness and away from individual organelle control (Fig. 2A and C(i)). Conversely, free-living plants retain large organelle genomes (Fig. 1, Fig. 2B and C(ii)) but have evolved strategies to mitigate the consequent mutational damage (reviewed below). As we will see, these strategies come at a new set of costs, further increasing the complexity of organelle genomes across plant life.

Figure 2: The hypothesised evolutionary tension in organelle genome structure. Bioenergetic organelles are chemically damaging environments. Transferring genes from organelle DNA to the nucleus embeds them in a safer environment at the cost of the ability of individual organelles to express genes or otherwise respond to local conditions. In (A), if a nuclear-encoded gene product is required by a specific organelle, it must be expressed then somehow transferred to that specific organelle. In (B), genes are encoded locally and can be expressed according to individual organellar priorities. Fluctuating environments place more variable demands on individual organelles, potentially favouring situations towards (B). (C) A Pareto front reflecting this tradeoff. Organisms can (i) retain fewer genes in organelles, increasing genetic robustness (due to nuclear features including decreased exposure to potential mutagens, more protective packaging, and higher-fidelity copying and proofreading machinery) at the cost of individual organelle control, or (ii) retain more genes in organelles, sacrificing genetic robustness to gain individual organelle control.

Dynamics of organelle populations in plant cells

This section will provide an overview of the major genetic and physical classes of dynamics elucidated to date in mitochondria and chloroplasts. Working at a mesoscopic level, it will focus on the possible ‘governing principles’ aligned with the cellular control of these organelle populations; some of these mesoscopic degrees of freedom are illustrated in Fig. 3.

Genetic populations of mitochondria in plant cells

We will begin with mitochondria. Several contrasts with the better-known mammalian mitochondrial system must be made clear from the outset. First, plant cells often contain fewer copies of mtDNA than mitochondria, so that some organelles contain no mtDNA [36, 37, 38]. Second, despite a pervasive picture of circular mtDNA molecules, it is likely that

circular mtDNA is the exception rather than the rule in plant cells [35, 41]. Rather, mtDNA exists in a structurally diverse range of linear and branched linear forms, the contents of which map to a circular structure [37, 41]. The specific forms involved change during plant development and have been observed in mung bean to increase in complexity from simple linear molecules to large rosette structures [109]. Third, plant mtDNA exhibits a dramatic separation of scales in its evolutionary rates. In contrast to mammalian mtDNA, plant mtDNA has a nucleotide substitution rate ('genic evolution') far below the nuclear rate [110]. However, the rate of genome structure evolution ('genomic evolution') in plant mtDNA is high, with dramatic reorganisations, duplications, and other large-scale changes to mtDNA occuring rapidly and repeatedly through evolution [110, 111, 19, 20, 112]. By contrast with other taxa, substantial gene transfer has occured into plant mitochondria from the plastid and nucleus, to the extent where mitochondria have been described as a 'dumping ground' for other genetic material [41]. Finally (and related to the above points), while recombination between mtDNA molecules in metazoa is thought to be very limited, indeed negligible [113], recombination between plant mtDNA molecules is frequent and common [114, 115, 116].

Mitochondrion	Size	Area □0.55 μm^2 *Arabidopsis* [49]; area 0.5-0.8 μm^2 spinach (#104802); volume 0.1-1.6 μm^3 spinach (#104801)
	Number	200-300 per cell *Arabidopsis* mesophyll [50]; 300 per cell young leaves, 400 per cell mature leaves *Arabidopsis* [36]; 500-600 per cell tobacco mesophyll protoplasts [102]
	Speed	0.6-3.4 μms^{-1} (up to 10 μms^{-1}) *Arabidopsis* root hair [103]; 0.1-0.5 μms^{-1} maize BY-2 cells [104]
	Genome size	368kb *Arabidopsis* (NC_037304); 222kb rapeseed (NC_008285.1); 1685kb cucumber (NC_01600[4-6].1); 11.3Mb *Silene conica* [105], 16kb *Chlamydomonas* (NC_001638)
	Genome number	40 per cell young leaves, 280 per cell mature leaves *Arabidopsis* [36]; 50 per cell *Chlamydomonas* (#107478)
Chloroplast	Size	Area 68 μm^2 spinach (#104798); volume 31 μm^3 spinach (#104800); volume 129 μm^3 *Chlamydomonas* (#110528)
	Number	100 per cell *Arabidopsis* mesophyll (#107029); 40-120 per cell *Arabidopsis* mesophyll protoplast [38]; 23 per cell palisade, 13 per cell spongy tissue poplar (#107028); 14-39 per cell *Heterosigma akashiwo* (#107032); 1 per cell *Chlamydomonas* (#107030)
	Speed	0.0015-0.0067 μms^{-1} *Arabidopsis* [106]; 0.005 μms^{-1} *Adiantum capillus-veneris* [107]
	Genome size	154kb *Arabidopsis* (NC 000932.1; #105918); 120-200 kb plants (#1022759, #111608); □130 genes plants (#106553); 204kb *Chlamydomonas* (NC_005353)
	Genome number	□600 per cell *Arabidopsis* [38]; 224 per chloroplast pea (#107108); 310-320 per chloroplast wheat (#107107); 500-10000 per cell tobacco (#102758); 80 per cell *Chlamydomonas* (#107478)

Table 1: Physical quantities pertinent to organelle populations. References starting with # are to the BioNumbers database [108]; references starting with NC are to annotated NCBI reference sequences. Species are given after values, including *Arabidopsis (thaliana)* and *Chlamydomonas (reinhardtii)*.

Figure 3: The multiscale biology of organelle populations. Physical and genetic processes influence organelle populations in plant cells. Small arrows reflect individual physical processes, the rates of which are to some extent controlled by the cell but are also influenced by stochastic effects. Longer arrows give an idea of the complex dependencies and influences of these physical and genetic processes at intra- and inter-cellular scales. We highlight two features in particular. (i) The coupling between physical

and genetic dynamics of organelles within cells. Physical dynamics contrain what genetic processes are possible: mtDNA recombination between molecules in different organelles, for example, requires colocalisation and fusion of those two organelles, and autophagy of an organelle removes genomes within it from the cellular population. (ii) The rates of these physical and genetic processes can be modified by selective pressures on cellular and organismal performance throughout evolution.

This additional ‘genetic operator’ of recombination gives rise to considerable complexity in the structure of cellular populations of mtDNA [115]. In metazoa, the dominant cellular picture is a set of molecules all highly similar to one full mtDNA sequence, with a mutational ‘cloud’ of variations on this theme [117]. By contrast, plant cells contain a ‘dynamic syncytium’ of differently structured mtDNA molecules in an evolving and interacting population [118, 50] with competition between multiple levels of selection (molecules, organelles, and cells) [95, 96].

The field of plant mitochondrial genetics contains several items of jargon that should be explained early. Different structures of mtDNA, perhaps involving rearrangements or truncations of genetic content, are called different *mitotypes*. Molecules of mtDNA with mitotypes that differ from the ‘full’ genome are called *sublimons*. These are referred to as existing *substoichiometrically* – that is, fewer sublimons exist than copies of the ‘main’ genome. Numbers of substoichiometric molecules are typically 10 − 1000 times lower than the number of main genome molecules [115]; in some cases, only a small fraction of plant cells contains sublimons [119]. *Substoichiometric shifting* [120] refers to the dynamic process by which the relative copy number of these sublimons changes, sometimes dramatically and over the course of one generation [121] (Fig. 4). This potential for rapid shifting can lead, for example, for one mitotype being amplified from rarity to dominance in a short period of time, perhaps during reproduction where organismal mtDNA copy numbers are low [122].

The dynamic structure of these cellular populations vary between species. Some *Brassica* species, for example, possess a relatively simple tripartite core system where a large mitotype coexists with two smaller mitotypes [123, 124]. Others, most notably in the *Silene* genus, partition their genome into dozens of different ‘chromosomes’ [125, 111]. This multichromosomal structure has been proposed as an adaptive feature facilitating a mode of sex to ameliorate mutational damage [111].

It has been postulated that the genetic content of the organelle population is partitioned into ‘master circles’ acting as complete repositories of genetic information, and ‘small circles’ containing a subset of genetic content [126, 123], although sequencing technology is revealing increasing nuance to this picture [127]. Analogous to this picture, it has been suggested that some mitochondria act as ‘genetic vaults’ [128] relatively insulated from DNA damage, while, in a division of labour, others are used, repaired but eventually abandoned, and replenished.

How frequently does recombination occur between mitotypes? In *Arabidopsis*, nonhomologous end-joining and recombination activity is rapid [129]. ‘Recombination surveillance’ machinery has been identified (notably involving the genes *Msh1* and *RecA3*) that controls the process of recombination in the mtDNA syncytium [130, 131, 129, 132]; when these are perturbed, recombination rates increase in *Arabidopsis* [133, 134]. It has been proposed that strand invasion occurs frequently and throughout the mtDNA genome in plants, but that *Msh1* prevents this leading to DNA exchange for any repeat regions under a cutoff size [129]. Notably, *RecA3* and *Msh1* expression is enhanced during flower

development where substoichiometric shifting has high potential to induce genetic changes [131].

The influence of recombination may be responsible for the dramatic difference between genic andgenomic rates of plant mtDNA evolution. Recombination and associated repair allows the avoidance of deletrious mutations, but comes at the cost of facilitating large-scale genomic changes, including the proliferation of selfish elements [12, 95, 96], and the risk of damaging structural changes to mtDNA. Ref. [112] proposes a more specific model for this link: DNA damage is converted into double-strand breaks, which are then fixed by various processes of varying accuracy (including non-homologous end joining and homologous recombination [130]). When an inaccurate fix induced change in a coding region, it is removed by selection, whereas large-scale changes can occur and propagate in non-coding regions. Such structural changes can yield dramatic phenotypes including cytoplasmic male sterility (see below). In general, then, recombination yields genetic advantages but necessitates cellular control mitigating against the proliferation of selfish elements and the appearance of damaging gene rearrangements.

This ‘no free lunch’ tradeoff has been the focus of theoretical developments using stochastic modelling and simulation [95, 96], and has led to the proposal of an umbrella theory for organelle inheritance strategies: an unstable tension between allowing recombination and disallowing it [12]. The adoption of different strategies on this spectrum – from no recombination, through occasional leakage, to ongoing frequent recombination – is discussed in Ref. [132].

The control of replication and degradation of plant mtDNA remains poorly understood [135, 136]. The rate of mtDNA replication, when it occurs during the cell cycle, and how it is controlled by the cell reflect open questions. Theory motivated by mammalian studies has proposed the ‘relaxed replication’ paradigm – where mtDNA replication is not tightly coupled to the cell cycle but is controlled to keep copy numbers somewhat stable [86, 87, 71]. MtDNA degradation is at least in part linked to mitophagy, the autophagy of mitochondria, which is an active area of investigation in plants [137].

Specific factors involved in the replication, repair, and recombination of mtDNA (reviewed, for example, in Ref. [138]) include DNA polymerases PolIA and PolIB, the Twinkle helicase, topoisomerases GyrA, GyrB, and TopI, recombinases RECA2 and RECA3, ssDNA-binding SSB1, SSB2, OSB1, OSB3, WHY2, and ODB1, ligase LigI, and the notable case of MSH1 above.

Physical populations of mitochondria in plant cells

Mitochondria are actively transported along actin [139, 140] and undergo diffusive and streaming motion [48, 140, 48, 49, 50, 51, 37, 47] (illustrated in Fig. 5A-B). Why does the cell invest energy in moving mitochondria so rapidly through the cell? One class of reasons is surely metabolic. Positioning organelles near where their functionality is required allows rapid responses to changing demands – this is observed across taxa, in the positioning of functional mitochondria near to energy-demanding regions like the growing bud in yeast [141] and the synapses in axons [142]. Plant metabolic pathways involving components from different organelles, including the important example of photorespiration [143], are facilitated by proximity between organelles. Mitochondrial-chloroplast colocalisation is commonly observed, notably in *Arabidopsis*, and has been linked to gradients of O_2 and CO_2 in the cell [48]. One key example of this positional control is that the relative position of these organelles is of central importance in the

emergence of Kranz anatomy in C_4 plants [144]. An early evolutionary step [145] in the emergence of C_4 photosynthesis is the relocation of mitochondria to inner bundle-sheath cell regions (near the vasculature) [146]. This positioning of organelles may allow the high levels of CO_2 efflux from mitochondria during photorespiration to be re-fixed by adjacent chloroplasts [144].

Figure 4: Risks arising from organelle DNA recombination. A simple hypothetical illustration of a recombining organelle system. + and − symbols denote illustrative population sizes. (A) Recombination facilitates a dynamic sharing of genetic information between, for example, a large molecular type and two smaller sublimons. This example illustrates the proliferation of selfish organelle DNA elements. In an extreme case, here one ‘selfish’ recombination product (2) contains only an origin of replication (OR) and limited additional content, and the other (3) contains more coding regions. The small selfish element will proliferate rapidly while the coding element disappears, and may come to dominate over the original element (1). (B) Stoichiometric shifting. Here a progenitor mitotype (1) exists with the tripartite system (2-3-4) existing substoichiometrically. One of the recombination products (3) contains a sterilising factor (white star). (i) Stoichiometric shifting can lead to the amplification of system (2-3-4) over mitotype (1), amplifying the sterilising factor and causing male sterility. Further shifting (ii) can reduce the presence of that recombination product, causing reversion to fertility. This is the model for CMS and reversion in common bean from Ref. [121].

In the context of this review, however, these physical behaviours also place strong bounds on the genetic dynamics of mtDNA in cells. MtDNA molecules are contained within their respective organelles in partly packaged structures called *nucleoids* [147, 50]. Clearly, the containment of mtDNA within organelles physically limits the genetic dynamics that can be supported. Molecules cannot recombine if they are not physically proximal; newly-replicated molecules will be tightly localised to their ‘parent’; molecules cannot be degraded without physical colocalisation with autophagic machinery [148, 137, 149]. At cell divisions, the genetic makeup of daughter cell organelles is exclusively determined by the physical inheritance of partitioned content during division [72, 70, 85]. These physical-genetic couplings necessitate a systems biology perspective to dissect.

Plant mitochondria often exist as discrete, individual organelles (Fig. 5), generally forming less fused structures than in metazoa, where large reticulated networks are often observed. Notably, plant mitochondria are known for undergoing ‘kiss-and-run’ dynamics [150, 149, 151]. This motion involves mitochondria transiently meeting and fusing, then partitioning and physically diverging.

Various stimuli, often associated with cell stress, alter the balance between fission (discrete mitochondrial elements) and fusion/expansion (elongated, expanded, or joined mitochondria). Observed across species, these include low oxygen [152], dark [153], physical and chemical cell death stimuli [154], and UV light [155]. Stress stimuli often induce mitochondrial clustering, expansion, and reduced motion. This behaviour may be linked with the activation of the permeability transition pore [154], a dramatic mechanism by which the mitochondrion releases its contents into the cytosol [156].

More extensive fusion is observed in particular circumstances in plants. One is in the *Arabidopsis* shoot apical meristem, where mitochondria form a reticulated ‘cage’ surrounding the nucleus prior to divisions [157]. Another is during *Arabidopsis* germination, where mitochondrial fusion is similarly transiently increased before subsequent

fragmentation [158]. Enhanced mitochondrial fusion is also observed in early protoplast culture in tobacco prior to cell divisions [102], including so-called ‘massive mitochondrial fusion’ associated with dedifferentiation [147]. ‘Condensation’ of mitochondria is also observed during barley pollen development [159, 160]. The perinuclear clustering of fused mitochondria observed in several of these situations is mirrored in other taxa; this has been suggested to optimise ATP supply to energy-demanding nuclear processes [157], or to optimise supply of nuclear-encoded components to mitochondria to facilitate biogenesis [158]. During germination-induced fusion in *Arabidopsis*, the stoichiometry of mtDNA sequences, and associated recombination activity, remains tightly controlled [158]. At the actual point of plant cell division, mitochondria are evenly distributed through the cytosol in tobacco [102] to assist in unbiased organelle partitioning between daughter cells [161].

Ref. [162] highlights that the *Arabidopsis* shoot apical meristem but not the root meristem or other tissues exhibit this cage-like fusion. The authors hypothesise that the SAM has a particular requirement for faithful partitioning of mtDNA to daughter cells because it is the ultimate source of the female gametes responsible for mtDNA heredity. The SAM-specific partitioning control thus preserves the stability of the mitochondrial population between generations.

Figure 5: Dynamic populations of organelles in plant cells. Timelapse confocal microscopy illustrates dynamics of mitochondria and chloroplasts in the hypocotyl of a 7-day *mtGFP Arabidopsis* [48] seedling. (A) Snapshot showing mitochondria (mtGFP, green), chloroplasts (autofluorescence, blue), and cell walls (propidium iodide stain, red). Scale bar is 10 μm. (B) Mitochondrial trajectories over 120s. Mitochondria exhibit a combination of directed and random, slow and fast motion, with dense and consistent movement around actin (i) and localised around chloroplasts (ii). (C) Chloroplast trajectories over 120s. Chloroplast motion is slower than mitochondrial motion and has a greater random component, with limited directed movement in the absence of light responses. Trajectories captured using Mosaic Particle Tracker software [163].

Outside of these special cases, why is mitochondrial fusion in plants so limited compared to other taxa? Kiss-and-run dynamics afford fewer opportunities for sharing organelle content than existence in a highly fused state (concurrently, the authors of Ref. [157] propose that the ‘cage-like’ fusion they observe can facilitate increased mtDNA recombination). This review hypothesises that *this physically limited opportunity for exchange could constitute a control mechanism limiting recombination and the emergence of selfish elements*. Additionally, maintaining mitochondria as discrete individuals allows more immediate identification and degradation of poorly-performing organelles. This picture bears some analogy to the fission-fusion axis for quality control in mammalian mitochondria, where individual mitochondria are functionally ‘assessed’ before being degraded [164].

Our understanding of how the physical degradation of plant mitochondria (mitophagy) is controlled remains limited. Whole-mitochondrion capture by the autophagosome and degradation in the vacuole has been observed in wheat when mitochondria are damaged or produce excess ROS [165]. During leaf senescence it appears that mitophagy removes mitochondria in *Arabidopsis* [166]. However, the rates of and cues for these processes remain unclear.

Specific genes involved in controlling mitochondrial dynamics in *Arabidopsis* continue to be elucidated [47]. A seminal study [49] identified five mutants, named *mmt1-2, bmt, nmt*, and

fmt, respectively for motley (heterogeneous), big, networked, and friendly (clustered) mitochondria. Perturbations to *nmt* and similar *elm1* [167] result in elongated mitochondria, suggesting perturbed fission dynamics. *FRIENDLY* has been characterised more recently and found to have dramatic effects on plant growth, mitochondrial functionality, and photosynthesis [150]. Dynamin-like genes *DRP3A* and *DRP3B* and *BIGYIN1* and *BIGYIN2* regulate mitochondrial size and number [168, 169, 170].

Genetic populations of plastids in plant cells

The genetic dynamics of ptDNA through plant life and development are not uncontroversial. PtDNA is contained in plastids, with typically dozens of ptDNA molecules per plastid, contained in nucleoids [171].As with mtDNA, ptDNA is often considered to map to a circular form, but physically consists of linear or branched molecules [172, 173, 174, 35].

The extent to which cellular copy numbers of ptDNA change during plant development has been the source of some controversy [175, 176]. Findings, chiefly from one research group, suggest pronounced changes in ptDNA copy number as protoplasts differentiate into chloroplasts, first increasing then decreasing [35], with this behaviour mirrored in plant development, with a several-fold increase in ptDNA per chloroplast in early seedling development, followed by a pronounced decrease in functional ptDNA levels as leaves age [177]. These results have attracted scepticism largely because of the high turnover of photosynthetic machinery encoded by ptDNA: how can chloroplast protein turnover be sustained without ptDNA? Experiments from other groups have not supported this picture, reporting instead (with a diversity of experimental techniques) that ptDNA levels decrease marginally or not at all [178, 179, 180, 181], or even increase, retaining ptDNA integrity [182] in ageing leaves.

PtDNA nucleoids may be tethered to a plastid membrane or membrane-free: an emerging hypothesis (reviewed in Ref. [35]) involves most activity (replication and repair) associated with the tethered nucleoids, with membrane-free molecules being prone to degradation. Once more, this picture bears some analogy to the fission-fusion axis for quality control in mammalian mitochondria, in the sense that a special state is used to protect organelles from degradation [164]. As with mitochondria, bioenergetic functionality may induce ptDNA damage in a progressive manner through development and time. Some observations are concurrent with this picture: in maize, DNA damage was observed to be lowest at the base of stalks and increased during leaf development in both light and dark conditions [183]. Again, this observation is subject to some controversy, with another group's results in a different maize cultivar finding little evidence for ptDNA damage [182]. However, even in the case of limited DNA damage, a picture is suggested where less active organelles are sequestered in less bioenergetically active cells, safer from damage and preserving genetic content for heredity, while more active organelles are exposed to damage (and repair) in more active cells.

PtDNA can undergo homologous recombination in plants and algae [184, 185, 186]. This fact is leveraged in numerous synthetic biology approaches to transform ptDNA for scientific, biotechnological, and potentially agricultural applications (reviewed in Ref. [45] and discussed below). Genes responsible for ptDNA recombination, including *RecA*, have been perturbed in algal, moss, and higher plants, decreasing the stability of cellular ptDNA populations [187, 186, 188, 189]. These recombination processes play important roles in repair and maintenance of ptDNA across plant species [190, 171]. However, the capacity for ptDNA to recombine does not imply a similar 'dynamic syncytium' picture to

mitochondria [171]. As plastids undergo fusion less readily than mitochondria (see below), and within-cell ptDNA heteroplasmy appears limited, the current picture is that ptDNA recombination between different 'chlorotypes' over cellular timescales is comparatively limited [191, 27]. Limited recombination has been observed between different plastid types in cells [192, 193, 184], with segregation separating rather than homogeneising these populations. Recombination-dependent replication of ptDNA has been suggested to account for diversity in ptDNA structure [64], and bioinformatic studies have suggested that rearrangements of gene order in ptDNA may provide adaptive advantages [194].

The within-cell genetic heterogeneity of ptDNA molecules is controversial, with studies in different species reporting presence or absence of ptDNA heteroplasmy (reviewed, for example, in Ref. [195]).The specific technological and bioinformatic pipelines used can lead to different interpretations of observations [196]. A comprehensive review of the appearance and proliferation of ptDNA mutants in higher plants appears in Ref. [191]. PtDNA degradation and recycling occurs during chlorophagy [197] (see below).

Specific factors involved in the replication, maintenance, and degradation of ptDNA in *Arabidopsis* have been recently reviewed [38]. These include MSH1, gamma polymerases, RecA proteins, TWINKLE, and the WHIRLY ssDNA-binding regulators. Notably, there is a large overlap between this set of factors and the above involved in the genetic dynamics of mtDNA. Comparable regulatory machinery thus influences the dynamics of the two organelle classes.

Physical populations of plastids in plant cells

Despite their substantially larger size compared to mitochondria, plastids are also dynamic organelles, albeit with lower rates of motion (Table 1, Fig 5). The motion of chloroplasts in response to light conditions has been well studied across species [52, 53]. Chloroplasts move away from intense light ('avoidance') and towards desirable levels of light ('accumulation'), balancing photosynthetic capacity against photodamage [198]. The motion of chloroplasts, in concert with that of other organelles, also seems geared to facilitate colocalisation between different classes of organelle [54]. As with mitochondria, chloroplasts have a plethora of additional physical and metabolic degrees of freedom. As with mitochondria, chloroplast positioning plays important facilitating roles in photorespiration and efficient photosynthesis, with the number, size, and position of chloroplasts differing dramatically in different cell types in C_3 and C_4 photosynthesis [144, 199].

Plastids divide, and modulate their copy number and compartment size, through fission [33]. Chloroplast division is tightly controlled to yield uniform daughter organelles [200]. Divisions involving other classes of plastid seem to be less physically constrained and give rise to a wider variety of physical forms [33].

Fusion of plastids, facilitating exchange and potentially interaction of macromolecules including ptDNA, is more controversial. Observations of 'stromules', elongated links between plastids, seemed for some time to imply that plastids were capable of fusing and exchanging content. Experiments with photobleaching have cast doubt on this idea [201], and while proteins may be exchanged via stromules [202], ptDNA nucleoids appear not to be [203]. Plastid fusion is observed in root-fungal interactions in tobacco and other species, when the arbuscule forms in root cells [204, 205, 206], where a plastid network forms, facilitate by stromule connections. This fusion has been hypothesised to be linked to an increased demand for plastid metabolic activity [206]. Outside this specific

circumstance, evidence for widespread fusion is limited [207], raising the question of what about arbuscule formation places such unique demands on plastid behaviour.

If mitochondrial fusion serves to homogeneise the cellular mtDNA population prior to divisions, how is ptDNA partitioned without pronounced fusion? Ref. [162] suggests that due to the larger size of plastids (and, implicitly, the fact that each plastid contains several ptDNA molecules), the ptDNA population is already more homogenised than the mtDNA population. At cell divisions, plastids adopt perinuclear positions [102] to assist in unbiased organelle partitioning between daughter cells.

Chlorophagy removes plastid content either ‘piecemeal’ or at the level of the whole organelle. This recycling is mediated by rubisco-containing bodies and senescence-associated vesicles; a recently-reportedadditional mechanisms involves chloroplast vesiculation in *Arabidopsis* [208] (reviewed in [197]). Chlorophagy is induced during senescence and as a response to abiotic stress [209]. Photodamaged chloroplasts are transported to the vacuole for degradation [210], suggesting an analogy with the function-dependent quality control of mitochondria through mitophagy [211]. Both photodamaged chloroplasts and dysfunctional mitochondria are important sources of reactive oxygen species in the cell, suggesting a common priority to remove these potentially damaging organelles from the cell.

Specific factors involved in the physical dynamics of plastid division are reviewed in Ref. [33]. Chloroplast division involves a contractile complex including FtsZ1 and FtsZ2, PDV1 and PDV2, ARC6, and ARC5/DRP5B. A control system analogous to the bacterial Min system, involving MinD1, MinE1, and ARC3 assists in the spatial regulation of chloroplast division. CLMP1 and CRL have been implicated in the later separation of chloroplasts after division. Factors involved in chloroplast motion are reviewed in Ref. [52] and include CHUP1, KAC, PMI1, PMIR1 and PMIR2, and THRUMIN1.

Synthesis: Organelles through a lens of evolutionary systems biology

While the rich modes of behaviour of these organelles are being increasingly revealed through experiments, many questions remain regarding the control and purpose of these processes. For example, why is organelle recombination common in plants but not animals? Why are mitochondria more heteroplasmic, dynamic, and prone to fusion than plastids? This section will attempt a synthesis of the genetic and physical behaviour we have summarised into a consistent picture. It must be underlined that this is a highly speculative endeavour, intended to generate discussion and hypotheses, rather than a claim of scientific fact.

Start with our hypothesised tension (Fig. 2): (i) removing genes from organelle DNA decreases their susceptibility to mutational damage via mutagens generated through organelle activity, while (ii) retaining genes in organelle DNA enhances organelle responses to fluctuating environments. Plants are immobile and so must deal with fluctuating environments *in situ*. Retaining higher numbers of organellar genes, and therefore higher control over individual organelles, may therefore be adaptive, by (ii). However, by (i), these genes will be damaged, necessitating ameliorative mechanisms. Further, the inability to evade environmental fluctutations will make these genes more susceptible to damage from mutagens produced through redox imbalance arising from bioenergetic activity. We can speculate that immobile organisms are under increased pressure to evolve mechanisms to ameliorate organelle DNA damage (Fig. 6A).

As we have seen, plant cells employ a (coupled) range of such mechanisms, including recombination-mediated repair, recombination-mediated exchange of genetic material between organelles, and 'divisions of labour', where some genomes are kept intact and safe for heredity and to sustain the organelle populations ('genetic vaults' of mtDNA, and less active plastids), while some are used and abandoned. This division of labour is supported by repair and by the physical control and distribution of organelles (Fig. 6B).

Figure 6: **Hypothesised synthesis of physical and genetic plant organelle control.** (A) Plants are immobile and thus subject to greater environmental fluctuations than motile organisms. These fluctuations are hypothesised to lead to increased potential for organelle DNA damage through redox activity, and an increased pressure to retain organelle genes for CoRR or alternative sensing and control. (B) This increased potential for damage requires mitigation, which occurs through 'division of labour' facilitated by recombination, repair, and abandonment. Plastids can sequester genetic content in less active organelles, repairing but eventually abandoning content in bioenergetically active organelles. Mitochondria are all active and must instead mitigate damage through physically-mediated exchange, surveillance, and repair.

If these hypotheses do reflect general principles of organelle behaviour, how can we explain the dramatic differences between mitochondria and chloroplasts in genetic and physical structure? One possibility stems from how mitochondria and plastids differ in their spread of bioenergetic activity. Mitochondria are 'always on': their metabolic, bioenergetic, and signalling pathways rely on an intact membrane potential generated by redox activity. Plastids have a set of forms that do not involve photosynthetic activity. In a coarse-grained picture, perhaps these less active forms can be regarded as 'safe' repositories for ptDNA. Then, if plastids can adopt such a 'safe' mode, there is no need for any further complexity.

PtDNA can be sequestered in safe plastids in less active cells, while 'unsafe' active chloroplasts function, gradually degrade their ptDNA (with some repair) and are eventually abandoned. If mitochondria are always active (and unsafe), there is no reliable 'genetic vault'. Then, following the hypothesised behaviour in Ref. [128], partitioning the genome between many actively recombining organelles, repairing or abandoning molecules when they get damaged, is a safer strategy. To quote from Ref. [128]: *unequal distribution of the mitochondrial genome between mitochondria with different functions would invoke a requirement for mitochondrial fusion and subsequent fission to provide mtDNA, mtDNA-encoded mRNA or protein to those bioenergetically active mitochondria without the capacity, or with a reduced capability, to provide for their own needs*.

Pursuing this idea, may the plant indeed leverage physical dynamics to control genetic dynamics of organelles? This sharing of genetic content is actively facilitated and controlled by the physical motion of organelles. Does rapid 'kiss-and-run' dynamics ensure that all organelles get a chance to 'see' a given gene? If the cell limits mitochondrial fusion to control rates of mtDNA recombination, kiss-and-run dynamics may be the most optimal alternative to allow this mitochondrial 'complementation' [55, 128].

An alternative explanation for recombination, also potentially linked to plants' immobility and consequent environmental fluctuations, is that nuclear genes like *Msh1* allow the control of recombination in response to environmental circumstances, allowing the reversible generation of genetic variation if desired [130].

Systems biology approaches, combining microscopy, genetic characterisation, and modelling, can test these hypotheses and shed new light on these evolutionary and

cellular connections.If this line of reasoning has merit, we would expect other immobile organisms to share some of these features with plants. Intriguingly, the few metazoans that have been observed to share mtDNA recombination machinery with plants are those with relatively immobile lifestyles (corals, sponges, and sea anemones [132]). Ref. [132] highlights that these species and plants also share a developmentally late partitioning of somatic and germline cells. This observation aligns with theoretical results suggesting that germline sequestration is driven by high mitochondrial mutation rate [212]. Within the speculative scheme in this article, this cell-to-cell division of labour may be ‘allowed’ because organelle-to-organelle division of labour protects organelle genetic integrity.

Further, in this scheme, we may expect plants that are less subject to environmental fluctuations to retain fewer organelle genes. Indirect potential evidence for this comes from recent observations in mistletoe, where some mitochondrial genes have been completely lost [100, 101]. Mistletoe’s parasitic lifestyle means that it is less dependent on its own intrinstic bioenergetic performance in fluctuating environments; the associated gene loss mirrors observations in other taxa, where parasitic organisms have lost substantial mitochondrial content (both genetic and metabolic) [213, 214]. Further exploration of gene retention (using large-scale genomic data) and recombination rates across plant species will help support or falsify these hypotheses.

Human exploitation of plant organelle populations

Clearly, the centrality of mitochondria and chloroplasts in plant metabolism mean that their value to the human sphere is as broad as that of plants themselves. But what aspects specifically of the behaviours summarised above are pertinent in agriculture and biotechnology? Perhaps the best-known phenotype directly associated with dysfunctional control of organelle genome populations is cytoplasmic male sterility (CMS). CMS is a trait conferred by the mitochondrial genome that compromises the ability to produce functional pollen, anthers, or male gametes (reviewed in [41, 42, 43, 44]). CMS has been observed naturally in over 150 species [215]. CMS is of central importance in crop breeding, allowing the creation of female plants that cannot produce viable male gametes, and hence the straightforward production of hybrid plants. Hybrid vigour or heterosis results in substantial yield increases from hybrids compared to their inbred precursors, with improvements of 15-50% possible [216], making hybrid formation highly agrinomically desirable.

CMS has been observed in many species and manifests through a range of mtDNA features acting as ‘sterilising factors’ and a corresponding and debated range of mechanisms. Perturbations to recombination surveillance can induce these factors, with, for example, the *Msh1* gene being the focus of several exciting translational advances exploiting the control of mtDNA populations for agricultural purposes in tomato and other species [217, 218]. CMS can result from substoichiometric shifting amplifying the low-level representation of a mitotype containing a sterilising factor (Fig. 4C) [124, 121, 130]. MtDNA alterations causing CMS include chimeric gene fusions, partial ORFs, and disruptions in gene orientation and promoter association [41]. These alterations typically affect the mitochondrial electron transport chain. CMS has been suggested to result from compromised energy supply (although an inducible mutant in *Arabidopsis* compromising ATP production did not mirror the CMS phenotype [219]), dysfunctional signalling, induction of programmed cell death, or cytotoxicity, although these mechanisms remain to be fully characterised.

An early harnessing of ptDNA populations arose from the fact that ptDNA mutants give rise to variegation – patterns of discolouration – in higher plants. This physical patterning depends on the type and the proliferation of the mutation (reviewed in Ref. [191]) and is an aesthetically valued trait in some ornamental plants.

Further, ptDNA is readily transformable and is experiencing growing use in biotechnology. Expressing genes of interest in plant or algal ptDNA can lead to high yields of desirable products (reviewed in [45] and [220]). Active areas of development involve introducing resistance traits to plants, and using chloroplasts as factories for vaccines, antibodies, and biofuel enzymes. In exciting recent work, for example, the complete metabolic pathway for artemisinic acid (the precursor for anti-malarial drugs) was introduced to tobacco, leading to plants producing 120mg artemisinic acid per kilogram [221].

Harnessing the genetic mixing induced by grafting [222, 223, 224], such engineered pathways can be introduced from a transformable species into other species [225] to avoid toxicity or to capitalise on other desirable properties. The nuances of inheritance of organelle DNA mean that these transgenes are readily containable and do not constitute germline changes to organisms, important features that may make organelle manipulation more palatable to regulators and the public.

Engineering the physical control of organelle populations is also a potential translational avenue, for example, for the ongoing goal of enhancing crop yields by re-engineering photosynthetic performance [226]. One facet of this target is the engineering of C_4 photosynthesis into C_3 plants [227, 228]. In recent work, the synthetic re-engineering of organelle development in rice (inducing large bundle-sheath chloroplasts) induced other C_4 traits including enhanced cell-to-cell communication via plasmodesmata [229]. As the repositioning of mitochondria is an early and central feature in the emergence of C_4 photosynthesis, perhaps the ability to artificially engineer mitochondrial position may open analogous doors to this grand target?

Much more speculatively, the central thesis of this article suggests another potential avenue of investigation of investigation. Organelle populations reflect an evolved tradeoff between genetic robustness and organelle control. Can we, in agricultural settings, manipulate the position that plants have adapted on this tradeoff to better suit human needs? For example, if organelle activity is limited in some plant tissues to protect some ptDNA for the purposes of heredity, can we instead sacrifice this ptDNA, producing less viable plants but increasing photosynthetic capacity? One interesting and potentially aligned result involved the overexpression of Golden2-like transcription factors in *Arabidopsis* leading to global induction of chloroplast biogenesis in the root, increasing CO_2 fixation and promoting phototrophic performance [230]. It is tempting to speculate that other re-engineering strategies may manipulate this evolved tradeoff for human gains.

Tools from systems and interdisciplinary biology

Even if the highly speculative synthesis above has merit, a plethora of other questions remain. To what extent do physical features (noise, discrete compartments, etc) limit how the plant controls its organelles? What control principles govern the replication and degradation of organelles? How are the feedback control signals that govern these behaviours transduced? Systems biology approaches can also help shed light on these questions.

With a particular view to evolutionary systems biology, an important class of open questions relates to the genotype-phenotype (GP) maps [57] of the complex organelle population system. In a system where heteroplasmy and multiple genome copies are present, the picture of a GP map becomes even more complicated: cellular phenotypes from protein complex structure to bioenergetic performance are potentially determined both by features of, and interactions between, many (organelle and nuclear) genotypes.

How can approaches from interdisciplinary, quantitative, and systems biology help elucidate these systems? Firstly, mathematical models of complex biological systems can be used to develop insight and intuition in noisy biological systems where experimental results are hard to obtain [82]. As described above in ‘Cellular noise and organelle populations’, such modelling work has provided general insights into the behaviour and principles underlying stochastic cellular populations of organelle genomes. While these mathematical results have direct and general implications for asexual organelle populations, further work (including consideration of how to parameterise such models [231]) is required to explore recombination as a cellular control strategy.

Another branch of quantitative modelling, the physical representation of organelles in the cell, remains challenging, largely due to the many factors that in principle need to be accounted for and parameterised, including cytoskeletal structure, concentrations of metabolites, and electrochemistry of organelles. However, even in the absence of fully-detailed physical models, important mechanistic insights can be gained from mesoscopic modelling. Coarse-grained studies are emerging that use generative models to simulate expected organelle dynamics under different hypotheses and circumstances, and compare the behaviour of these simulations to experimental observations. These approaches have revealed, for example, the consequences of perturbing the control of mitochondrial dynamics on organelle ultrastructure [150]. The influence of the physical location of organelles on their inheritance has also been considered in jointly theoretical and experimental work [79]. A ‘low-hanging fruit’ here is the question of how mitochondrial dynamics influence the genetic structure of the cellular population. For example, does the highly dynamic ‘kiss-and-run’ system facilitate efficient sharing of limited mtDNA content across the physical population of organelles? Modelling work can also shed light on the evolutionary principles governing organelle populations [10]. Powerful theoretical studies over the last few years have revealed how competition between different levels of selection in organelle-cell systems drive the evolution of sex [232] and uniparental inheritance [233]. Further work revealed that the theoretical fitness advantage of uniparental inheritance depends on wider population context, suggesting a tension that may result in the emergence of different inheritance modes [234]. A multiscale theoretical study identified mitochondrial fission-fusion, genome segregation, uniparental inheritance and paternal leakage to explore how non-recombining organelles can mitigate mutational damage [235], complementing and expanding earlier mtDNA models for recombination [95, 96]. In work aligned with the central thesis of this article, theory has shown that selection for mitochondrial quality can drive the evolutionary emergence of a distinct germline (as observed in animals, and as opposed to the somatic gametogenesis in plants) [212]. This work proposes that high mtDNA mutationrates require a division of labour, in the sense that a ‘safe’ germline is sequestered for heredity while less ‘safe’ somatic cells engage in bioenergetic function.

Next, systems biology approaches to harness and integrate the expanding volumes of ‘omics’-style data can help shed light on several underlying questions. The genes controlling the physical and genetic dynamics of organelles are increasingly being elucidated. Regulatory interactions controlling these genes, revealed through systems

biology, can help explore hypotheses for the fundamental principles underlying cellular control of organelles. The integration of gene expression data for bioenergetic genes from the organelles and nucleus will help dissect organelle-nuclear co-operation, and support or falsify the various hypotheses underlying organelle gene retention and control (CoRR, redox sensing, etc). Integrated characterisation of genome structure, gene expression and, metabolic poise will help elucidate the mechanisms by which CMS becomes manifest [41].

At the evolutionary level, the increasing volume of genomic data available from sequencing initiatives can be harnessed by systems biology approaches to quantify support for evolutionary hypotheses [18]. More generally, systems biology offers the tools to quantitatively investigate hypotheses and mechanisms in this world of noisy dynamics and uncertain measurements [236, 237]. Mirroring other fields of biology, the study of organelle dynamics is transitioning from a traditional ‘t-test’ picture – where a difference in two cases is reported – to a ‘model selection’ picture, where different hypotheses are quantitatively tested for their ability to explain the observed data. In particular, the ‘multiple causes’ problem [238, 239], well known in ecology and evolution but less central in cell biology, is pertinent to these multiscale questions and is best dissected through systems approaches.

Conclusions

Physically embedded, dynamic, stochastic populations of organelle genomes are constantly evolving and moving in plant cells. These organelles feed the world and are natural targets for biotechnological approaches to improve yields and bioengineering processes. A host of open questions remain from the evolutionary to the cellular levels, quantitative answers to which will open new research and development avenues. Researchers from complex systems, stochastic processes, control theory, evolutionary physics, biochemistry, genetics, cell biology, and metabolism, among others, will find fertile ground for valuable research here. The tools of systems biology, from large-scale characterisation of cellular behaviour to mathematical modelling, can help learn about these multiscale problems. I hope that this article will serve as a valuable reference for, and to stimulate discussion with, interdisciplinary researchers approaching this exciting field.

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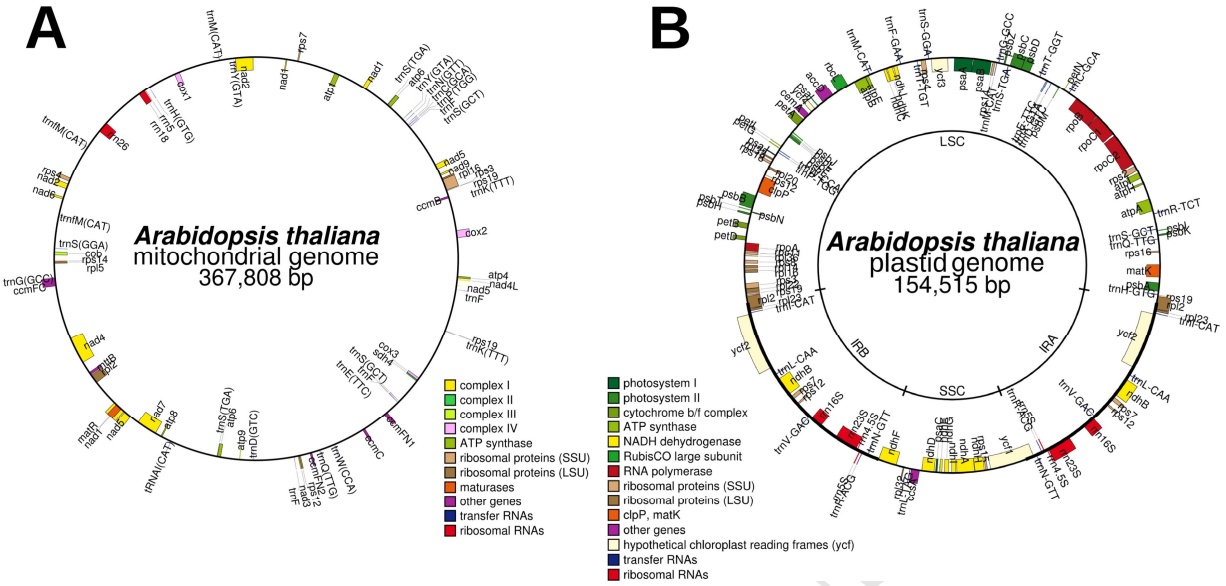

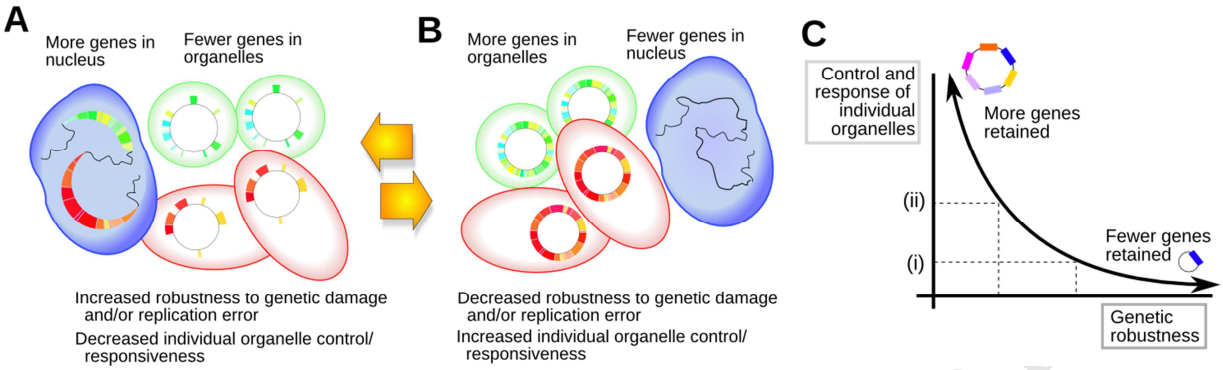

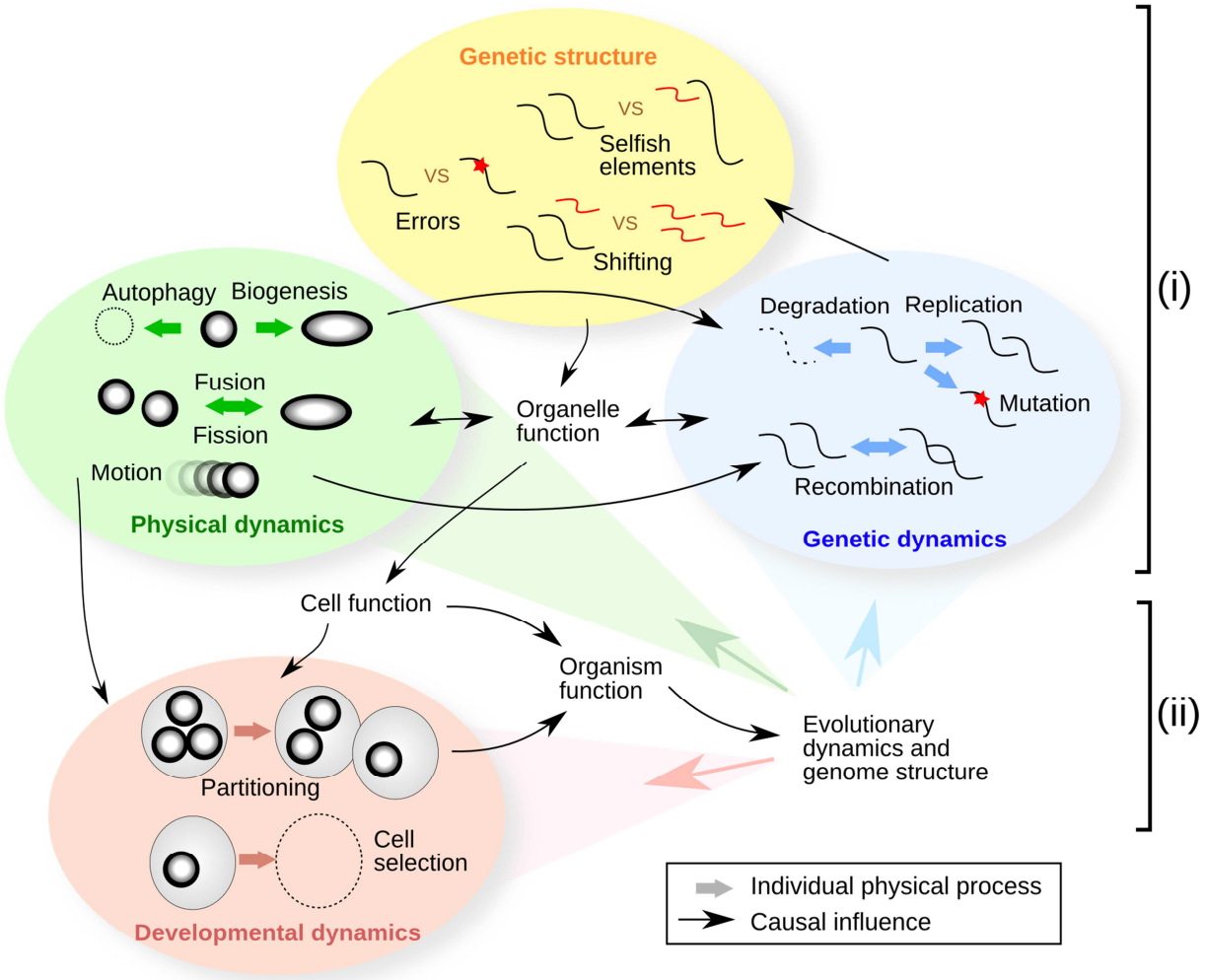
Genetic structure
vs
Selfish elements
vs
Errors
vs
Shifting
Autophagy
Biogenesis
Fusion
Fission
Motion
Physical dynamics
Organelle function
Degradation
Replication
Mutation
Recombination
Genetic dynamics
(i)
Cell function
Organism function
Evolutionary dynamics and genome structure
Partitioning
Cell selection
Developmental dynamics
(ii)
Individual physical process
Causal influence