Plasticity and scaling through multinucleation: a key adaptation to challenging environments

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Abstract

Multinucleate cells, single cells containing multiple nuclei in a shared cytoplasm, are found across the eukaryotic tree of life. Having evolved independently in fungi, plants, protists, and animals, they thrive in environments ranging from nutrient-poor deep-sea sediments to dynamic soil microhabitats and host tissues. Multinucleate organization enables spatial specialization without internal partitions and rapid scaling of metabolic or transcriptional capacity, allowing organisms to forage across patchy resources, withstand physical stress, and respond quickly to environmental fluctuations. Yet multinucleation also brings challenges, including diffusion limits, nuclear coordination, and the potential for genetic conflict. Its repeated emergence, often in lineages that have also evolved multicellularity, points to shared cellular, structural, and regulatory prerequisites shaped by ecological pressures. Here, we integrate perspectives from cell biology, ecology, and evolution to demonstrate that multinucleation is not a rare anomaly but a fundamental organizational strategy. Recognizing these systems as adaptive responses to environmental constraints provides a framework for uncovering general principles of cellular organization, evolution of life cycle strategies, and the diversification of complex life.

Introduction

Multinucleate cells, those containing multiple nuclei within a shared cytoplasm, are a widespread yet underappreciated feature of eukaryotic life. They occur across diverse lineages, including fungi[1,2], protists[3–6], plants and algae[7–11], and animals[12–14] (Figure 1; Supplementary Table 1). Their repeated, independent origins across the tree of life point to strong selection for cellular architectures that achieve large-scale integration without constructing and maintaining intercellular boundaries. The ecological and functional diversity of multinucleate cells, from terrestrial to marine, parasitic to free-living, underscores their remarkable adaptive capacity.

Despite their breadth, multinucleation is often treated as an exception rather than a robust evolutionary strategy that addresses complex biological demands. Here, we recast multinucleation as a recurrent solution to the challenges of scaling and coordination in diverse living systems. Across lineages in which multinucleation appears, there seems to be a set of core features that confer several functional advantages that help to reconcile the challenges of being large, spatially heterogeneous, or metabolically active. These features include: (1) enhanced biosynthetic capacity, allowing rapid scaling of transcription and translation; (2) localized control, where spatially distinct nuclei respond to local conditions; (3) capacity for long-range intracellular transport, partially offsetting the diffusion constraints inherent to large cells; (4) life-cycle flexibility, enabling shifts between unicellular, syncytial, and multicellular stages; and (5) economic growth, permitting size increase without the energetic costs of constructing and maintaining cell–cell junctions.

Multinucleation is not the only solution to the challenge of expanding biosynthetic capacity beyond the limits of mononucleate, haploid organization. Polyploidy is an alternative solution. While multinucleation distributes genomes among multiple nuclei within a shared cytoplasm, polyploidy concentrates extra genome copies within a single nucleus[15–17]. Interestingly, these strategies are not mutually exclusive, as polyploid nuclei can be found in multinucleate cells[18,19]. Despite their shared capacity for genomic amplification, multinucleation and polyploidy differ in organization and control. Polyploidy centralizes regulation within one enlarged nucleus, favoring coordination but limiting spatial specialization, whereas multinucleation enables local transcriptional activity and responsiveness to spatial cues[16,20–23]. In that regard, multicellularity and aggregative multicellularity might be conceptually closer to multinucleation, as all expand function by combining an increased number of nuclei with spatial control. Yet they do so through different structural solutions: multicellularity partitions nuclei into discrete cells, allowing division of labor and compartmentalized regulation, whereas multinucleation maintains all nuclei within a shared cytoplasm, enabling rapid coordination and resource sharing across large cellular domains. Although these architectures solve similar challenges, each offers distinct advantages and disadvantages.

This perspective aims to explore the ecological and evolutionary roles of multinucleation, highlight the features that enable persistence of multinucleation across diverse niches, and examine the benefits and trade-offs of multinucleate versus multicellular strategies. By considering the cellular routes by which multinucleation forms and the underlying molecular machinery that enables it (Box 1) and examining the environments in which multinucleation is advantageous (Box 2), we can identify general principles that unify multinucleate cells across the tree of life, ultimately positioning multinucleation as a distinct form of cellular complexity.

Unifying principles of multinucleation and their evolutionary significance

Multinucleation has arisen repeatedly across eukaryotes because it provides a set of powerful functional advantages that allow organisms to scale metabolism, regulate spatially distributed processes, coordinate activity across large cytoplasmic domains, and flexibly adjust their architectures in response to environmental and developmental demands. Although the organisms that use these strategies inhabit strikingly different ecological niches, each feature of multinucleation supports a shared underlying principle: distributing genomic, metabolic, or regulatory capacity across space enables cells to achieve levels of dynamic coordination and performance that would be difficult for uninucleate cells or conventional multicellular organization.

The cellular machinery enabling multinucleation is deeply conserved, drawing on core eukaryotic capacities involving cytoskeletal remodeling, vesicle trafficking, membrane fusion, and transcriptional regulation [24–26]. The recurrence of these mechanisms across independent lineages underscores the convergent nature of multinucleation as a versatile and efficient solution to the challenges of scale, coordination, and adaptation. Below, we articulate how each functional principle aligns with specific ecological or developmental contexts.

1. Enhanced biosynthetic capacity and transcriptional scaling

Changes in genome copy number can directly influence RNA and protein abundance [27,28], linking transcriptional output to cellular architecture and biosynthetic capacity. By increasing nuclear number, multinucleate cells amplify genomic and transcriptional output without the cost of constructing additional membranes or intercellular junctions. Additionally, the distribution of multiple nuclei throughout the cytoplasm can permit localized gene expression, allowing different regions of the same cell to have distinct biosynthetic profiles. This spatial organization distinguishes multinucleation from polyploidy, in which transcriptional amplification remains confined to a single region.

The advantages of biosynthetic scaling are realized in strikingly different ecological and developmental contexts. In terrestrial fungi and plasmodial slime molds, dispersed nuclei support rapid expansion across heterogeneous substrates, fuel the metabolism required for extensive exploratory networks, and allow organisms to exploit resource hotspots[1,29–34]. In animals, myonuclei positioned along the length of a muscle fiber enable localized transcriptional responses and maintain the high protein turnover required for contractility and regenerative capacity [23,35,36]. For siphonous algae like *Caulerpa* and *Bryopsis*, which inhabit nutrient-poor and mechanically demanding marine environments, multinucleation provides the biosynthetic capacity necessary to support their remarkable macroscopic growth[11,37–40]. Despite their ecological differences, these systems illustrate the same core principle: scaling biosynthesis through nuclear multiplication allows organisms to match metabolic output to environmental opportunity, whether for growth or structural maintenance.

2. Distributed spatial regulation within a shared cytoplasm

A feature of many large multinucleate cells is their ability to achieve spatial organization in the absence of physical partitions. Instead, nuclei can act as distributed regulatory hubs, each capable of adopting distinct transcriptional states that respond to local cues[22,23,41–44]. Additionally, microtubule-based forces help maintain nuclear spacing and organization, coordinating cell cycle progression and spatial independence, as reported in both *Drosophila* embryos and *Ashbya gossypii* fungi [24,45].

Spatial regulation extends beyond transcriptional control. RNA-binding proteins and cytoskeletal transport systems ensure mRNAs are translated where they are needed, while phase-separated RNA–protein condensates fine-tune translation in space and time. In *Ashbya gossypii*, Whi3-dependent condensates position mRNAs near growth zones, linking nuclear division to polarized growth[46,47]. Localized translation allows selective protein synthesis to defined cytoplasmic regions[48], a strategy conserved from fungi to mammals and essential for cell-cycle control and polarity[46,49].

Post-translational modifications further contribute to spatial control by modulating protein activity in response to local signals. Phosphorylation, ubiquitination, glycosylation, and SUMOylation rapidly alter protein stability or function, contributing to localized responses. In multinucleate trophoblast syncytia, for instance, growth factors such as IGF and LIF integrate MAPK/ERK and JAK/STAT signaling to coordinate proliferation and differentiation[50].

3. Active transport and circulation in large continuous cells

Growing beyond the scale at which diffusion alone can sustain metabolism requires active transport systems that redistribute metabolites, organelles, and signals over large distances[51]. Multinucleate cells meet this challenge by coupling cytoskeletal networks to cytoplasmic streaming, enabling rapid long-range movement within a continuous cytoplasm[52–54]. Like multinucleate cells, neurons employ motor-driven transport along cytoskeletal tracks; however, microtubule-based kinesin and dynein motors are used for highly directional cargo delivery rather than actin-based bulk flow[55].

The benefits of long-range transport in multinucleate cells are evident in siphonous algae, such as *Caulerpa*, *Bryopsis*, and *Halimeda*, where actomyosin-driven streaming moves resources across macroscopic thalli [10,11,38,39,53]; in *Physarum* plasmodia, where rhythmic contractions coordinate signaling and nutrient flow over centimeter to meter scales[54,56,57]; and in xenophyophores and other deep-sea foraminifera, where active transport maintains homeostasis under nutrient-poor, low-temperature, and high-pressure conditions [4,58–61]. Such active circulation systems enhance metabolic efficiency and extend cellular function beyond the limits of passive diffusion.

4. Architectural flexibility across life-cycle transitions

Many organisms in multinucleate lineages alternate between uninucleate and multinucleate stages, giving them the ability to reorganize their growth and reproductive strategies in response to environmental conditions. This flexibility buffers against environmental fluctuations such as nutrient scarcity, desiccation, or host limitation. *Physarum* transitions between uninucleate amoebae and multinucleate plasmodia depending on nutrient availability[62,63]; parasites such as *Plasmodium* spp. generate multinucleate schizonts to maximize progeny within host cells before generating invasive uninucleate stages[44,64]; and ichthyosporeans, such as *Sphaeroforma arctica*, undergo coenocytic growth (see also Box 1) prior to cellularization and dispersal[5]. Fungi likewise alternate between multinucleate hyphae and uninucleate spores during stress or reproductive transitions [32,65]. In each case, this capacity to alternate between architectures allows organisms to balance resilience, reproduction, and resource use across fluctuating environments.

5. Energetic considerations of cytoplasmic continuity

Multinucleation may offer an energetically efficient route to building and maintaining large or spatially complex cellular architectures. By expanding a shared cytoplasm rather than dividing it into multiple smaller cells, multinucleate systems bypass some of the structural and metabolic costs associated with forming membranes, junctions, and extensive intercellular signaling machinery. While the energetic consequences of this organization are not fully resolved across all lineages, several biological systems illustrate how reduced compartmentalization can coincide with rapid growth, structural continuity, or efficient resource allocation.

In aseptate fungal lineages such as Mucoromycota and Glomeromycota, extensive multinucleate networks traverse heterogeneous substrates and fluctuating nutrient microhabitats. Many Glomeromycota form arbuscular mycorrhizal symbioses, exchanging nutrients with over 80% of terrestrial plants, where multinucleation facilitates nutrient exchange with hosts and redistribution within the fungal network [29,30,66–68]. In siphonous algae, macroscopic thalli are formed from a single multinucleate cell. These lineages sustain large-scale morphologies, and their continuous cytoplasm supports rapid wound healing and flexible resource transport, features that may reduce the energetic burden associated with constructing multicellular tissues[37,38,40]. Deep-sea xenophyophores, which achieve extraordinary cell sizes in extreme conditions, also exhibit coenocytic organization; the distributed nuclei support localized metabolic control, which is thought to be an energy-efficient strategy that is ideal for survival in such environments [4,58,59].

Multinucleation and multicellularity as alternative scaling strategies

Multinucleation and multicellularity represent two distinct yet functionally overlapping solutions to the problem of biological scale. Multinucleate cells internalize the collective, housing many nuclei within a continuous cytoplasm, while multicellular organisms externalize it, distributing nuclei across discrete but coordinated cells. In many lineages, they coexist or alternate across life cycles as both achieve division of labor, metabolic efficiency, and coordinated behavior, albeit to different extents[17,69,70].

Multinucleate architectures

Multinucleate organization achieves multicellular-like integration without constructing membranes between nuclei or relying exclusively on intercellular signaling. These cells can coordinate activity across large spatial domains and redistribute resources rapidly. Continuous cytoplasm also allows signals, organelles, and metabolites to move freely, supporting cohesive behavior across regions that would otherwise require complex intercellular communication and intercellular transport structures. However, this architecture is not without costs. As cytoplasmic volume increases, diffusion becomes limiting, placing greater demands on active transport systems. Maintaining order across a large, continuous cell requires precise regulation of nuclear activity, cytoskeletal organization, and spatial patterning. Local disturbances, such as infection, can propagate more readily through a shared cytoplasm than in multicellular tissues. Despite these trade-offs, there are specific ecological niches where multinucleation excels, including heterogeneous substrates that require long-range foraging, mechanically strenuous environments, or intracellular niches for immune evasion. In such contexts, the ability to integrate many nuclei within one continuous cytoplasm offers a robust and adaptable solution to challenges that might be difficult for either uninucleate cells or fully partitioned multicellular tissues to meet.

Colonial and aggregative architectures

Colonial and aggregative forms, by contrast, preserve individuality while achieving collective behavior. Independent cells interact through adhesion and chemical signaling, forming transient assemblies that can readily form or dissipate in response to environmental cues. In choanoflagellates, bacterial lipids induce clonal rosette formation; in *Dictyostelium*, starvation triggers chemotaxis-driven aggregation reinforced by kin recognition and policing[71]. Such collectives can reduce predation, as seen in *Phaeocystis* mucilaginous colonies, while enhancing resource capture[72,73]. These systems are flexible and facilitate cooperation without permanent commitment[74]. Their limitations lie in slower and less precise coordination, mechanical fragility, and vulnerability to cheaters, yet they thrive in fluctuating or resource-limited environments where reversible collectives offer adaptive advantages.

Multicellular architectures

Multicellular architectures, meanwhile, allow cooperation through stable connections and differentiation, producing tissues composed of specialized cell types integrated by signaling networks. This strategy supports deep functional specialization, robust homeostasis, and the capacity for complex, scalable body plans[75–78]. However, these benefits come at a high energetic cost: maintaining intercellular communication and tissue integrity may slow reproduction, increase energy expenditure to construct such tissues, and reduce reversibility once cells are terminally differentiated. Consequently, multicellularity dominates in stable, structured habitats where the benefits of long-term specialization outweigh the flexibility lost through commitment.

Evolutionary convergence in organizational strategies

Together, these architectures illustrate that evolution repeatedly converges on a set of solutions to the same fundamental challenges, e.g., scaling, coordination, and conflict mediation, each balancing autonomy and integration in distinct ways. Multinucleation likely achieves speed and flexibility by connecting processes in a unified cytoplasm; colonial systems favor adaptability through loose cooperation; and multicellularity establishes stability through division of labor. These possibilities remain hypotheses, and comparative work will be essential to test how these architectures truly differ in function and constraint. Nonetheless, the recurrence and coexistence of these strategies across lineages reveal a shared evolutionary logic: the drive to extend the reach of cooperation without forgoing control (Figure 2).

Phylogenetic distribution of multinucleation and multicellularity

It is striking that multinucleation is found almost exclusively in eukaryotic lineages that also evolved some form of multicellularity, either true multicellularity or aggregative behaviors (Figure 1; Supplementary Table 2). This co-occurrence suggests that the underlying cellular toolkits required for coordinating multiple nuclei may overlap with those needed for coordinating multiple cells, potentially predisposing certain lineages to both architectures[69,76,77]. Even groups dominated by unicellular species, such as the Excavata, show this dual potential: *Acrasis kona* exhibits an aggregative life stage capable of collective behavior, while other excavates, *Multisulcus malaysiensis*, can produce multinucleate cells [79,80].

There are a few notable exceptions, however. In Metamonada, which includes diplomonads such as *Giardia duodenalis*, multinucleation occurs despite an apparent lack of multicellular or aggregative forms; the characteristic binucleate state of diplomonads represents a minimal yet genuine multinucleate architecture[81]. This deviation from the broader pattern raises interesting questions about why multinucleation can evolve in the absence of multicellular capacity in this lineage. Additionally, it appears that there are only two lineages, Haptophyta and Glaucophyta, that form colonial structures but lack known multinucleate cells. The haptophyte *Phaeocystis* [72,73] and the glaucophyte alga *Cyanoptyche gloeocystis*[82] both form colonies. Together, these exceptions point to important gaps in our understanding and highlight avenues of exploration to test which cellular features enable or constrain these architectures.

Unresolved relationships between multinucleation and multicellularity

Whether multinucleation precedes, parallels, or follows multicellularity remains to be resolved [17,83,84]. Both enable coordination and division of labor, yet through contrasting architectures, one continuous, the other compartmentalized. Multinucleation may have served as a functional precursor to multicellularity, allowing spatial patterning to emerge within a shared cytoplasm before the emergence of intercellular junctions. Alternatively, the molecular toolkits for multicellular coordination may facilitate the emergence of multinucleation as a derived trait. Understanding this relationship offers insight into one of life's major evolutionary transitions.

Where multinucleate states arise through fusion events, their relationship to multicellularity is potentially derived rather than ancestral. Formation of syncytia (see also Box 1), such as trophoblasts and skeletal muscle fibers, depends on adhesion proteins like cadherins[85], which themselves trace back to the earliest holozoans. Choanoflagellates already encode cadherins, C-type lectins, and tyrosine kinases[86], which could suggest that the molecular toolkits for cell-cell adhesion and communication predate animals and were later co-opted for syncytial fusion. From this perspective, syncytial multinucleation represents a reconfiguration of multicellular organization within a continuous cytoplasm.

By contrast, coenocytic multinucleation, arising from nuclear division without cytokinesis, may offer a more direct route to multicellularity, bypassing adhesion-based mechanisms, but utilizing other shared mechanisms that rely upon the actomyosin network, for example. Notably, ichthyosporeans, close unicellular relatives of animals, display coenocytic growth phases in which nuclei divide synchronously within a shared cytoplasm before cellularization[5,87,88]. In this regard, multicellularity may represent a reconfiguration of coenocytic multinucleation, in which a continuous cytoplasm containing multiple nuclei became progressively partitioned into discrete, interacting cells.

It remains possible that multinucleation and multicellularity arose, not as successive stages of complexity, but as parallel strategies that independently emerged along routes to the same problem: how to organize genomes and their outputs into a coherent whole. These observations invite further comparative studies into the molecular and physical bases of large-scale coordination across eukaryotes.

Mitotic mechanisms and the evolution of cellular architectures

If multinucleation and multicellularity represent parallel routes to large-scale coordination, the diversity of mitotic mechanisms offers a window into how these architectures evolved. Across eukaryotes, mitosis tends to align with cellular organization, where multinucleate lineages predominantly exhibit closed mitosis, in which the nuclear envelope (NE) remains intact, and uninucleate lineages favor open mitosis, involving NE breakdown[89–92]. Closed mitosis allows multiple spindles to operate independently within a shared cytoplasm, preserving local control amid cytoplasmic continuity. In contrast, open mitosis facilitates stronger coupling between nuclear and cytoplasmic processes, an arrangement well suited to uninucleate cells.

Intriguingly, some lineages retain the capacity for both. *Physarum*, for instance, performs open mitosis in its uninucleate amoebal form but closed mitosis in its multinucleate plasmodium [62,63]. This dual capacity within a single organism highlights how mitosis can evolve contextually, depending on life-cycle stage and cellular organization. The ability to accommodate both open and closed mitosis may have facilitated evolutionary transitions between uninucleate, multinucleate, and multicellular states, linking the mechanisms of division to the broader challenge of organizing genomes or cells in space and time.

Challenging the notion of individuality

Multinucleate cells challenge the classical view of the uninucleate cell as the fundamental unit of life, revealing that biological individuality can emerge at multiple organizational levels. Selection may act on individual nuclei, genetically identical or distinct, on specific cytoplasmic domains, or on the organism as a whole. This multilevel perspective parallels discussions in evolutionary biology about individuality in colonial organisms, holobionts, and symbiotic systems [17,75,78,93–96].

When genetically distinct nuclei coexist in a shared cytoplasm, as in fungal heterokaryons, cooperation and conflict become central concerns. Such chimeric states can persist for long periods, raising questions about how selection operates within a shared cytoplasm and how policing mechanisms suppress selfish nuclear lineages that might otherwise exploit communal resources. Various control strategies have been reported to suppress such conflicts, including selective nuclear degradation, in which incompatible nuclei are targeted for programmed destruction[97]; compartmentalization through septal plugging, which isolates heterokaryotic cells and prevents the spread of incompatible nuclei[98]; and nucleophagy under starvation, whereby specific nuclei are degraded to redistribute nutrients and ensure colony survival[68]. Together, these mechanisms restrict access to shared cytoplasmic goods and maintain cooperative function within multinucleate cells[99–102].

Not all nuclear heterogeneity arises from genetic differences. Nuclei in multinucleate cells can divide asynchronously, occupy distinct transcriptional states, and respond differently to local signals despite sharing cytoplasm[1,32,41,44]. This nuclear autonomy enables regional specialization, localized mRNA gradients, spatially restricted translation, and the formation of subcellular zones with distinct physiological functions. Such internal patterning demonstrates that discrete cellular partitions are not necessary for spatial complexity.

Conclusion

Multinucleate cells are more than biological anomalies; they are recurrent, versatile solutions to fundamental problems of scale, coordination, and adaptability. Spanning the tree of life, from deep-sea sediments to developing embryos and intracellular parasites, they compel us to reconsider multinucleation as a robust strategy for growth, resilience, and survival. By enabling distributed control, spatial compartmentalization without partitions, and rapid scaling of transcriptional capacity, multinucleation redefines where the line between a single cell and a collective truly lies.

This makes multinucleate systems uniquely powerful for exploring cooperation and conflict at the subcellular level, testing theories of individuality and evolution, and uncovering organizational principles that illuminate eukaryotic origins to modern biotechnological design. Emerging tools now make it possible to interrogate these questions with unprecedented precision: live imaging and spatial transcriptomics reveal nuclear dynamics in real time, single-nucleus sequencing and multi-omics profiling resolve heterogeneity within a shared cytoplasm, and quantitative modeling and synthetic reconstruction can experimentally test how coordination emerges among many genomes.

Together, these advances promise to transform our understanding of multinucleate life, not merely as a cellular curiosity, but as a window into the general principles of biological organization. As we begin to investigate and understand these systems in molecular detail, we are invited to rethink not only how cells function, but what it means to be a cell in the first place.

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BOX 1. Mechanisms of multinucleation across eukaryotes

Multinucleation predominantly arises via two mechanisms: (1) nuclear division without cytokinesis and (2) cell–cell fusion, with additional mechanisms occurring under stress or disease, such as failed mitotic exit. Although these processes operate in distinct developmental, ecological, or pathological contexts, they rely on modifications of conserved cellular machinery, including actin and microtubule networks, membrane remodeling complexes, and cell cycle regulators, adapted to the demands of each lineage[24–26].

Nuclear division without cytokinesis (coenocytic growth)

Definition:
Karyokinesis proceeds while cytokinesis is delayed or absent, producing many nuclei within a continuous cytoplasm.

Key features:
- Rapid amplification of nuclear number
- Expansion of biosynthetic capacity
- Maintenance of a physically continuous intracellular space

Representative examples:
- Filamentous fungi (e.g., *Aspergillus*, *Fusarium*): coenocytic hyphae spanning heterogeneous substrates[32,103,104].
- Plant endosperm (e.g., *Arabidopsis*): early coenocytic stage supports nutrient provisioning [7,105–107].
- Plasmodial slime molds (e.g., *Physarum*, *Fuligo*): centimeter- to meter-scale multinucleate plasmodia[62,108–110].
- Early insect embryos (*Drosophila*, *Tribolium*, *Nasonia*): rapid, synchronous nuclear divisions before cellularization[111,112].
- Siphonous marine algae (*Caulerpa*, *Bryopsis*, *Halimeda*): macroscopic single cells dependent on long-range cytoplasmic transport [11,37,113].

Cell–cell fusion (syncytium formation)

Definition:
Individual uninucleate cells fuse, merging into a shared cytoplasm with multiple nuclei.

Key features:

- Rapid increase in cytoplasmic volume
- Combines cells without nuclear proliferation
- Requires fusogens, adhesion proteins, and actomyosin remodeling

Representative examples:

- Skeletal muscle: myoblast fusion produces elongated, multinucleated myofibers with high contractile output[13,114].
- Placenta: trophoblast fusion generates the syncytiotrophoblast, a specialized multinucleate barrier for maternal–fetal exchange[50,115].
- Immune system & tissue repair: macrophage fusion produces osteoclasts (bone resorption) and multinucleated giant cells during chronic inflammation[116,117].

Failure of mitotic exit or cytokinesis (pathological multinucleation)

Definition:

Errors in cell-cycle regulation (e.g., spindle defects, telomere dysfunction, or cytokinetic failure) produce multinucleated cells. The same machinery enabling functional multinucleation can also generate pathological states when dysregulated.

Key features:

- Typically associated with disease or stress
- Reflect breakdowns in checkpoints rather than adaptive strategies

Representative examples:

- Cancer: multinucleated giant cells indicate genomic instability; may precede clonal evolution or senescence[118–121].
- Stress-induced defects: hypoxia, chemotherapeutic agents, or mechanical strain induce cytokinesis failure in mammalian cells[122,123].
- Viral infections: viral fusogens induce pathological syncytia (e.g., measles, SARS-CoV-2), disrupting tissue integrity[124,125].

Nuclear division dynamics within multinucleate cells

Definition:

Once multinucleation is established, nuclear cycles may proceed synchronously, parasynchronously, or asynchronously. Division dynamics allow multinucleate cells to balance biosynthetic output with energetic constraints, demonstrating that nuclear autonomy is itself an adaptive layer of multinucleate organization.

Key features:

- Regulated by local metabolic conditions, cytoskeletal organization, and signaling gradients
- Reflect tuning between global coordination and local autonomy

Representative examples:

- Synchronous: early *Drosophila* embryos, generating thousands of nuclei with tight temporal control[112].
- Parasynchronous: *Aspergillus nidulans* nuclei divide in parasynchronous waves[104]
- Asynchronous: *Plasmodium falciparum* schizonts, enabling rapid proliferation in nutrient-limited host cells[44,64].
- Stress-modulated asynchrony: observed in filamentous fungi and nutrient-limited mammalian cells; divisions desynchronize to spread energetic demand[100,126].

Summary

Across eukaryotes, multinucleation arises through coenocytic growth, cell–cell fusion, or failed cell-cycle exit. Although mechanistically distinct, these processes rely on conserved cytoskeletal and membrane systems and have been repeatedly adapted to support growth, rapid expansion, performance, immunity, parasitism, and developmental patterning. Together, these mechanisms reveal that multinucleation is not an anomaly but a fundamental and flexible cellular strategy enabling organisms to integrate function across space, time, and environmental complexity.

Box 2. Ecological niches favoring the evolution of multinucleation

The ecological context in which an organism evolves strongly influences the development and persistence of multinucleate cells. Environmental factors such as nutrient availability, substrate structure and heterogeneity, and predation pressure impose selective constraints that can favor shared cytoplasmic organization. In such settings, multinucleation offers a versatile strategy for sustaining growth, coordinating metabolism, and maintaining resilience under fluctuating or resource-limited conditions.

Terrestrial ecosystems

Terrestrial ecosystems, particularly soils and decomposing organic matter, are physically complex, highly heterogeneous environments. Nutrients occur in patchy microhabitats, microbial communities are dense, moisture levels fluctuate, and substrates can be mechanically resistant. Organisms must navigate steep chemical gradients, shifting hydration cycles, and episodic resource pulses. Together, these features create a mosaic landscape where growth depends on continually responding to local and rapidly changing conditions.

Aquatic ecosystems

Aquatic environments, both marine and freshwater, present a very different set of constraints. Water supports large, extended cell shapes but also exposes organisms to turbulence and constantly fluctuating nutrient availability. Many habitats are oligotrophic; others are periodically mixed or disturbed by sediment flow. Deep-sea settings add high pressure, low temperatures, and chronic nutrient scarcity. Across these ecosystems, resource landscapes are shaped by fluid motion rather than substrate structure, and chemical signals disperse quickly, creating dynamic and often unpredictable conditions.

Intracellular parasitic niches

Intracellular parasitic niches are tightly enclosed, nutrient-limited, and under constant immune surveillance. Within spaces like erythrocytes, hepatocytes, or algal cytoplasms, movement is restricted and resource access is finite. Parasites must replicate efficiently within a fixed space while avoiding detection, which, together with spatial confinement, strongly shapes how growth and division are organized in these environments.

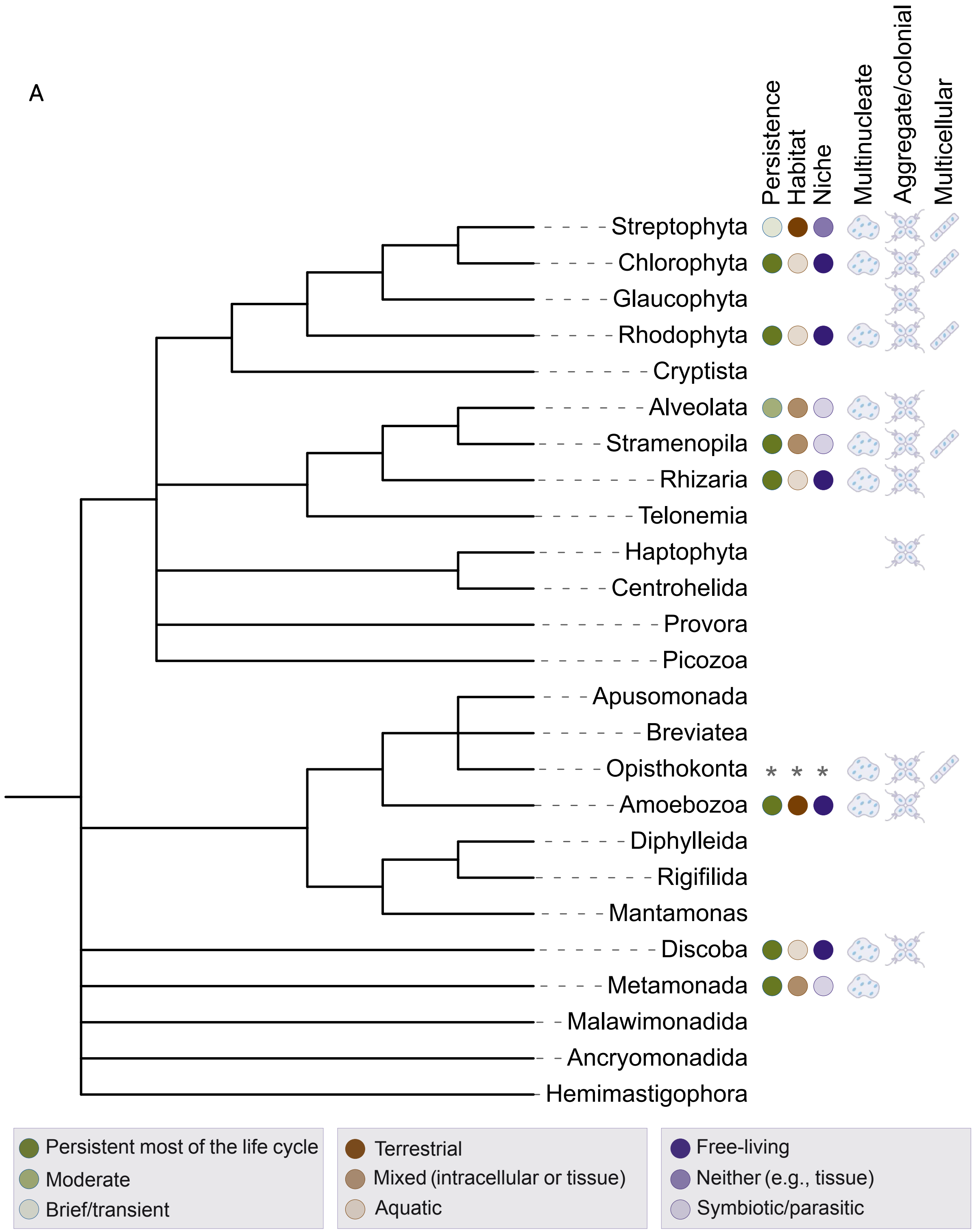
Transitional and fluctuating niches

Some organisms occupy habitats that shift rapidly over space or time. Seasonal environments, transient substrates, dispersal phases, and transitions between aquatic and benthic zones all impose fluctuating conditions. In these settings, organisms often benefit from flexible life cycles capable of switching between different cellular architectures. Transitional niches also include stress-induced states, which can be triggered by desiccation, hypoxia, or chemical damage, in which cells temporarily reorganize their growth dynamics, nuclear behavior, or genome content.

Developmental contexts

Multinucleation also arises in developmental settings where rapid expansion, intense biosynthetic demand, or coordinated activity across large cellular domains is required. Early embryogenesis often involves rapid nuclear divisions before cellularization, specialized tissues must accumulate resources quickly, and contractile or absorptive epithelia rely on coordinated gene expression across extensive cytoplasmic territories. These developmental niches impose tight temporal constraints distinct from those experienced by free-living cells.

A



Persistence
Habitat
Niche
Multinucleate
Aggregate/colonial
Multicellular
Streptophyta
Chlorophyta
Glaucophyta
Rhodophyta
Cryptista
Alveolata
Stramenopila
Rhizaria
Telonemia
Haptophyta
Centrohelida
Provora
Picozoa
Apusomonada
Breviatea
Opisthokonta
* * *
Amoebozoa
Diphylleida
Rigifilida
Mantamonas
Discoba
Metamonada
Malawimonadida
Ancryomonadida
Hemimastigophora
Persistent most of the life cycle
Moderate
Brief/transient
Terrestrial
Mixed (intracellular or tissue)
Aquatic
Free-living
Neither (e.g., tissue)
Symbiotic/parasitic

B

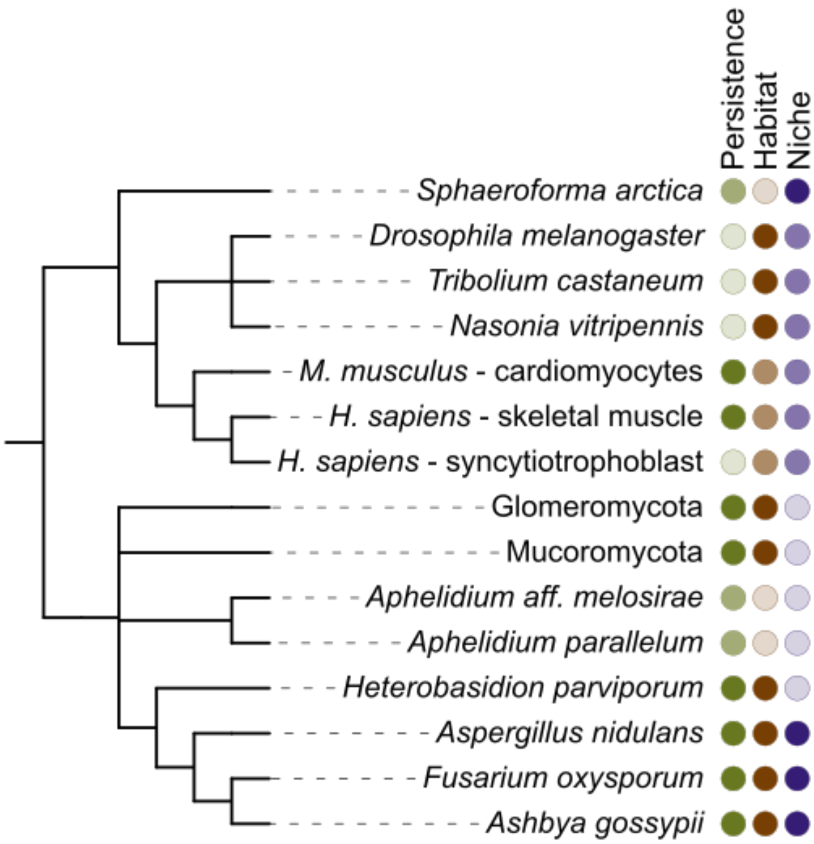


Figure 1. Ecological and organizational distribution of multinucleation across the eukaryotic tree of life.

- **(A)** A collapsed eukaryotic tree of life illustrating the phylogenetic breadth of multinucleate, colonial/aggregative, and multicellular architectures across major eukaryotic clades. For each lineage, three ecological attributes are annotated using color-coded circles: persistence (green), habitat (brown), and niche (purple). Icons to the right indicate whether the lineage contains multinucleate, aggregate/colonial, and/or multicellular forms. The figure highlights the repeated and phylogenetically widespread emergence of multinucleation across eukaryotes, as well as its co-occurrence with the other architectures.
- **(B)** Expanded view of Opisthokonta, showing finer-scale annotation of fungi, animals, and closely related protist lineages. The panel highlights the diversity of multinucleate architectures within this clade, from fungal coenocytes to animal syncytia, and illustrates how persistence, habitat, and niche categories vary even among closely related taxa.

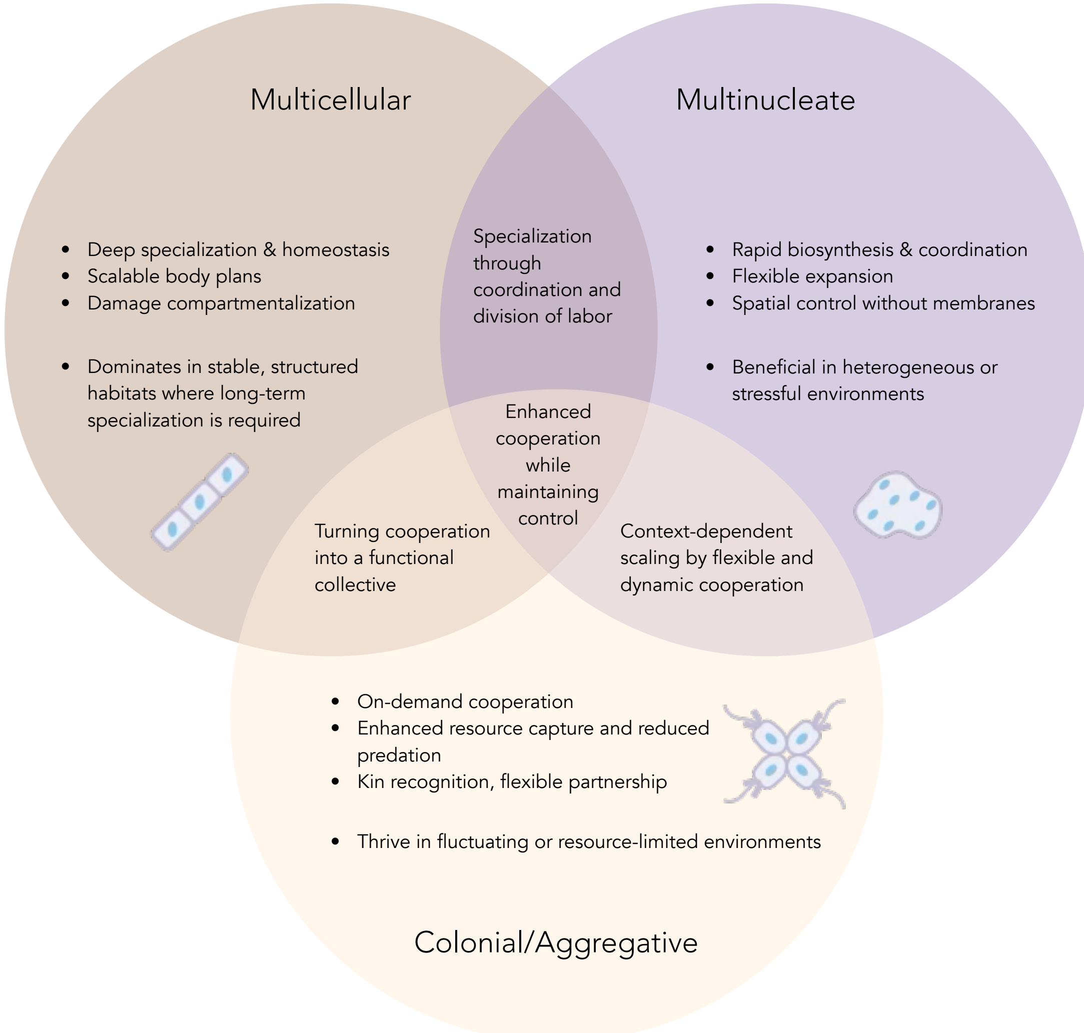


Figure 2 Conceptual relationships among multinucleate, multicellular, and colonial/aggregative organizational strategies.

Venn diagram summarizing the shared and distinct organizational principles of three major eukaryotic architectures that solve problems of coordination and scaling in different ways. Multinucleate cells integrate multiple nuclei within a continuous cytoplasm, achieving rapid coordination and regionalized function. Multicellular organization achieves long-lasting cooperation through stable adhesion, developmental patterning, and division of labor, enabling specialization. Colonial or aggregative forms maintain individuality while coordinating behavior through reversible adhesion and signaling, allowing flexible responses to environmental fluctuations. Overlapping regions highlight convergent strategies: enhanced cooperation while maintaining internal control, specialization through coordinated division of labor, and context-dependent scaling via dynamic cooperation.

Group	Species	Niche 1=Symbiotic/Parasitic 2=Neither (e.g., tissue) 3=Free-living	Habitat 1=Aquatic 2=Mixed (intracellular or tissue) 3=Terrestrial	Persistence 1=Transient 2=Moderate 3=Persistent	Justification	
Alveolata	*Plasmodium falciparum*	1	2	2	Parasitic; internal environment spanning mosquito and vertebrate hosts; multinucleate schizogony is a major proliferative stage	64,127
Amoebozoa	*Physarum polycephalum*	3	3	3	Free-living in terrestrial habitats; large multinucleate plasmodium is the dominant vegetative stage.	62
Amoebozoa	*Didymium iridis*	3	3	3	Free-living in terrestrial habitats; large multinucleate plasmodium is the dominant vegetative stage.	128
Amoebozoa	*Fuligo septica*	3	3	3	Free-living in terrestrial habitats; large multinucleate plasmodium is the dominant vegetative stage.	128
Streptophyta	*Arabidopsis thaliana* - endosperm	2	3	1	Plant tissue (neither free-living nor symbiotic); terrestrial; syncytial endosperm is an early, transient stage before cellularization.	7
Chlorophyta	*Caulerpa* spp.	3	1	3	Free-living marine siphonous algae; entire thallus is a long-lived multinucleate coenocyte.	113
Chlorophyta	*Bryopsis* spp.	3	1	3	Free-living marine siphonous green algae; coenocytic organization persists throughout the vegetative body.	11
Chlorophyta	*Halimeda opuntia*	3	1	3	Free-living marine coenocytic alga; multinucleate siphonous tissues form persistent calcified segments.	10
Chlorophyta	*Halimeda cuneata*	3	1	3	Free-living marine coenocytic alga; multinucleate structure maintained through most of the life cycle.	37
Discoba	*Chaos* spp. (*Chaos illinoisense*)	3	1	3	Free-living freshwater amoebae; trophic cells are large, multinucleate, and persist as such.	80
Metamonada	*Giardia duodenalis*	1	2	3	Parasitic/commensal in vertebrate intestines; host-internal environment; binucleate trophozoite is the main feeding stage.	81
Opisthokonta	*Aphelidium aff. melosirae*	1	1	2	Algal parasite; aquatic; multinucleate plasmodium forms during infection but is not long-term persistent.	129
Opisthokonta	*Aphelidium parallelum*	1	1	2	Algal parasite; aquatic; multinucleate plasmodium forms during infection but is not long-term persistent.	130
Opisthokonta	*Sphaeroforma arctica*	3	1	2	Free-living; aquatic; coenocytic growth spans a notable but not full portion of the life cycle.	5
Opisthokonta	*Aspergillus nidulans*	3	3	3	Free-living terrestrial filamentous fungus; vegetative hyphae are long-lived and multinucleate.	104
Opisthokonta	*Fusarium oxysporum*	3	3	3	Soil fungus and plant pathogen but ecologically free-living; hyphae are persistently multinucleate.	32
Opisthokonta	*Ashbya gossypii*	3	3	3	Free-living filamentous fungus; highly multinucleate hyphae persist through vegetative growth.	46
Opisthokonta	*Heterobasidion parviporum*	1	3	3	Fungal pathogen; hyphae persist for long periods.	101
Opisthokonta	Mucoromycota	3	3	3	Symbiotic terrestrial fungi with coenocytic hyphae; multinucleation is a stable vegetative condition.	66

Opisthokonta	Glomeromycota	1	3	3	Symbiotic arbuscular mycorrhizal fungi; terrestrial; extensive multinucleate hyphae persist throughout association with host plant.	30
Opisthokonta	*Drosophila melanogaster* - embryo	2	3	1	Embryo (neither free-living nor symbiotic); terrestrial; syncytial blastoderm is an early, transient embryonic stage.	111
Opisthokonta	*Tribolium* - embryo	2	3	1	Embryo (neither free-living nor symbiotic); terrestrial; syncytial blastoderm is an early, transient embryonic stage.	14,111
Opisthokonta	*Nasonia* - embryo	2	3	1	Embryo (neither free-living nor symbiotic); terrestrial; syncytial blastoderm is an early, transient embryonic stage.	111
Opisthokonta	*Mus musculus* - cardiomyocytes	2	2	3	Cardiac tissue; multinucleation/bi-nucleation is stable	19
Opisthokonta	*Homo sapiens* - skeletal muscle	2	2	3	Multinucleate muscle fibres within tissue; myofibres are long-lived syncytia.	13
Opisthokonta	*Homo sapiens* - syncytiotrophoblast	2	2	1	Placental tissue; syncytiotrophoblast remains multinucleate over the course of pregnancy.	115
Rhizaria	*Reticulomyxa filosa*	3	1	3	Free-living foraminifer; aquatic; extensive multinucleate reticulated cell body is long-lived.	131
Rhizaria	Xenophyophores	3	1	3	Free-living deep-sea foraminifera; aquatic; giant multinucleate coenocytes persist for long durations.	58
Rhizaria	Chlorarachniophytes	2	1	3	Mixotrophic protists with integrated endosymbionts; aquatic; reticulate multinucleate stages are persistent.	132
Rhodophyta	*Scinaia articulata*	3	1	3	Free-living marine red alga; multinucleate cells persist through vegetative growth.	133
Stramenopila	*Protoopalina intestinalis*	1	2	3	Symbiotic/commensal inhabitant of vertebrate intestines; internal habitat; multinucleate form persists within host gut.	3

Supplementary Table 1. Ecological and biological attributes of multinucleate taxa shown in Figure 1.

Table summarizes the ecological niche, habitat type, and persistence of multinucleate states for all representative taxa included in Figure 1. Each organism is scored along three categorical axes: Niche (1 = symbiotic/parasitic, 2 = neither (e.g., tissue), 3 = free-living), Habitat (1 = aquatic, 2 = mixed (intracellular or tissue), 3 = terrestrial), and Persistence (1 = transient multinucleate stage, 2 = moderate portion of life cycle, 3 = persistent or dominant life-stage). For each taxon, a brief justification is provided describing the ecological or developmental context in which multinucleation occurs, alongside the relevant citation(s). The table highlights the broad diversity of environments in which multinucleate architectures arise, from free-living coenocytes and filamentous fungi to intracellular parasites and transient developmental syncytia, and provides the dataset underlying the categorical annotations in Figure 1.

	Multinucleate	Multicellular	Aggregate/colonial	
Stramenopila	*Phytophthora infestans*	*Laminaria digitata*	*Glossomastix chrysoplasta*	Example
	Oertel & Jelke 1986[134]	Thomas et al. 2014[135]	O'Kelly 2002[136]	Citation
Alveolata	*Plasmodium falciparum*	-	*Zoothamnium niveum*	Example
	Klaus et al. 2022[44]	-	Clamp & Williams 2006[137]	Citation
Rhizaria	*Allogromia laticollaris*	-	*Guttulinopsis vulgaris*	Example
	Timmons et al, 2024[138]	-	Brown et al. 2012[139]	Citation
Telonemia	-	-	-	Example
	-	-	-	Citation
Haptophyta	-	-	*Phaeocystis pouchetii*	Example
	-	-	Estep et al. 1990[73]	Citation
Centrohelida	-	-	-	Example
	-	-	-	Citation
Cryptophyta	-	-	-	Example
	-	-	-	Citation
Katablepharida	-	-	-	Example
	-	-	-	Citation
Palpitomonas (Cryptista)	-	-	-	Example
	-	-	-	Citation
Glaucophyta	-	-	*Cyanoptyche gloeocystis*	Example
	-	-	Kies 1989[82]	Citation
Chloroplastida	*Caulerpa taxifolia*	*Arabidopsis thaliana*	*Volvox barberi*	Example
	Menzel 1987[113]	Sørensen et al. 2022[7]	Balasubramanian & McCourt 2021[140]	Citation
Rhodophyta	*Griffithsia monilis*	*Porphyra umbilicalis*	*Bangia sp.*	Example

	Hong et al. 2023[141]	Brawley et al. 2017[142]	Cao et al. 2018[143]	Citation
Ancoracysta (Ancoracysta/Provora)	-	-	-	Example
	-	-	-	Citation
Picozoa	-	-	-	Example
	-	-	-	Citation
Apusomonada	-	-	-	Example
	-	-	-	Citation
Breviates	-	-	-	Example
	-	-	-	Citation
Opisthokonta	*Neurospora crassa*	*Drosophila melanogaster*	*Fonticula alba*	Example
	Roper et al. 2011[2]	Vergasolla et al. 2018[112]	Toret et al. 2022[144]	Citation
Amoebozoa	*Physarum polycephalum*		*Dictyostelium discoideum*	Example
	Burland et al. 1993[62]		Du et al. 2015[71]	Citation
Diphylleida (Diphyllatea)	-	-	-	Example
	-	-	-	Citation
Rigifilida (CRuMs)	-	-	-	Example
	-	-	-	Citation
Mantamonas (CRuMs)	-	-	-	Example
	-	-	-	Citation
Discoba	*Multisulcus malaysiensis*		*Acrasis kona*	Example
	Prokina et al. 2025[80]		Sheikh et al. 2024[79]	Citation
Metamonada	*Giardia duodenalis*			Example
	Sagolla et al. 2006[81]			Citation
Malawimonadida	-	-	-	Example
	-	-	-	Citation
Ancyromonadida	-	-	-	Example

	-	-	-	Citation
Hemimastigophora	-	-	-	Example
	-	-	-	Citation

Supplementary Table 2. Distribution of multinucleate, multicellular, and aggregate/colonial architectures across major eukaryotic lineages.

Table summarizing the presence or absence of three organizational strategies: multinucleation, multicellularity, and aggregative/colonial architectures across the eukaryotic clades included in Figure 1. Multinucleate encompasses coenocytes and syncytia; Multicellular refers to tissue-forming multicellularity; and Aggregate/colonial includes collectives such as mucilaginous colonies or amoebozoan aggregators. Representative taxa and citations are listed where these architectures are documented.

The table complements the comparative phylogeny in Figure 1, showing that multinucleation and multicellularity commonly co-occur within the same lineages. Several clades deviate from the dominant patterns (e.g., Metamonada, which exhibit multinucleation without known multicellular or colonial states, and Glaucophyta or Haptophyta, which form colonies but lack confirmed multinucleate forms). These exceptions highlight promising avenues for testing which cellular toolkits enable, constrain, or bias the evolution of different large-scale architectures.

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