**PROBLEMS & PARADIGMS**

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# New tools suggest a middle Jurassic origin for mammalian endothermy

## Advances in state-of-the-art techniques uncover new insights on the evolutionary patterns of mammalian endothermy through time

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**Abstract**

We suggest that mammalian endothermy was established amongst Middle Jurassic crown mammals, through reviewing state-of-the-art fossil and living mammal studies. This is considerably later than the prevailing paradigm, and has important ramifications for the causes, pattern, and pace of physiological evolution amongst synapsids. Most hypotheses argue that selection for either enhanced aerobic activity, or thermoregulation was the primary driver for synapsid physiological evolution, based on a range of fossil characters that have been linked to endothermy. We argue that, rather than either alternative being the primary selective force for the entirety of endothermic evolution, these characters evolved quite independently through time, and across the mammal family tree, principally as a response to shifting environmental pressures and ecological opportunities. Our interpretations can be tested using closely linked proxies for both factors, derived from study of fossils of a range of Jurassic and Cretaceous mammaliaforms and early mammals.

**KEYWORDS**
endothermy, fossil, mammal evolution, metabolism, palaeontology, synapsid

## INTRODUCTION

The evolution of endothermy is widely regarded as one of the most important transitions in vertebrate palaeontology.[1] Occurring at least twice, in the lineages of living mammals and birds, the development of this condition fundamentally changes an organism's relationship with its environment. "Warm-blooded" endotherms are largely released from the reliance on environmental heat that typifies "cold-blooded" ectotherms, that must modify their behaviour to regulate their body temperature (Tb) using environmental means (e.g., warming via basking or cooling via hiding). A stable Tb is integral for regulating a host of metabolic processes, and its maintenance in endotherms irrespective of external temperature (homeothermy), allows them to remain active in colder environments and darker periods than ectotherms.[2] Precise control over organ temperature also allows endotherms a higher degree of complexity of important bodily processes.[3,4]

The physiological differences between ectotherms and endotherms are not dichotomous, and both classifications include a broad range of Tbs and metabolic rates.[5–7] However, living endotherms typically exhibit three characteristics that are measurably different to ectotherms.[8] Endotherms (a) possess a basal metabolic rate (BMR), the minimum rate of metabolic expenditure required to maintain a

consistent Tb. This is significantly higher than the equivalent resting metabolic rate (RMR) of ectotherms that indirectly regulate Tbs using external means. This results in (b) an endothermic ability for visceral organs to metabolically create a constant core temperature that does not significantly alter with varying ambient temperatures. Finally, (c) endotherms are capable of considerably more sustained aerobically intense activity and higher maximum metabolic rates (MMRs) than nearly all ectotherms, allowing more sustained amounts of aerobically demanding activity.

These physiological advantages come at a cost to endothermic animals, as their elevated metabolisms impose a nutritional demand up to an order of magnitude higher than for ectotherms of comparable size.[9] This trade-off has made untangling the long-term adaptive pathways and selection pressures of endothermic evolution an intriguing but much debated realm of enquiry for researchers. The study of physiological evolution is hampered by a lack of direct evidence, as it relates primarily to soft organs (viscera and muscles) that are rarely fossilised. A series of indirect indicators and metrics have been suggested to represent the physiological status of fossil animals.[1] Application of these through the fossil record has allowed inferences to be made regarding the causation, pattern, and timing of endothermic development along the lineages leading to mammals and birds. However, the indirect and often contradictory nature of many lines of evidence has led to considerable debate surrounding these factors, and uncertainty as to why and when endothermy evolved.[10]

However, the metrics and tools involved have matured, and now provide more nuance to their accounts of physiological development amongst fossils. Here, we discuss the primary hypotheses for endothermic evolution amongst the synapsids, the lineage leading to living mammals (Box 1), and review the latest innovations and lines of evidence used to plot the pattern of physiological evolution through their fossil record (Figure 1).

## EARLY CLUES AND MODERN REVIEWS ON THE ORIGIN AND EVOLUTION OF ENDOTHERMY AMONGST SYNAPSIDS

The predominant hypotheses for the origin of endothermy amongst synapsids, as summarised by Kemp,[8] centre around the relative timing of BMR versus MMR evolutionary increases above the ancestral ectothermic values. Less frequently discussed, but often implicit, is the idea that both evolved in at least partial lockstep with each other—the correlated progression hypothesis.[8,15] Most hypotheses argue that either enhanced aerobic activity and elevated MMR, or thermoregulation and elevated BMR, was the initial aspect of endothermy primarily selected for, with the other either passively or directly changing secondarily or in lockstep. Hypotheses include the aerobic scope hypothesis (aerobic scope is the difference between BMR and MMR) suggesting that higher MMR was originally selected for to allow more sustained aerobically demanding activity,[16–18]; and the thermoregulatory hypothesis, suggesting that higher BMR was initially selected for enhanced thermoregulative control.[19–21] Hypotheses within either

camp differ as to the predominant selective driver, and use differing evidence as support. Many lines of evidence have been re-analysed and re-interpreted over time, with successive innovations and additional fossils[10,13,22,23] (Figure 1). See Benton[1] for further details.

## Evidence and hypotheses for increasing thermoregulation and BMR

One characteristic used to suggest that increased thermoregulation and BMR was the primary driver of endothermic evolution is the increase in encephalisation quotient (EQ; the ratio between brain-mass and body-mass) through the synapsid fossil record. Endotherms typically have EQ values an order of magnitude larger than ectotherms, with enlarged, more complex brains that require more precise control of their metabolic systems.[24,25] It remains unclear whether brain development facilitated physiological development by allowing greater coordination and ecological complexity, or benefited from physiological development providing more energy, or that both mutually supported each other via correlated progression.[8] While the accuracy of EQ estimates of non-mammaliaform taxa is hampered by the lack of ossification of much of the braincase, recent studies suggest an overall increase in EQ through the cynodont lineage.[23] However, a recent paper[26] questions the assumption that brain-body allometry is a stable scaling relationship, showing that shifts in this slope are often characterised by marked changes in body size and not solely due to selection on brain size. Whether there was a "burst" of increased EQ in mammaliaforms,[27] a relatively steady increase,[11] or more complex pattern[28] remains undetermined (Figure 1).

Another pattern of endocranial evolution across the cynodont-mammaliaform transition is the development of discrete regions of the brain, indicative of increased olfactory and tactile sensitivity, potentially linked to nocturnality.[27,28] The presence of sensory vibrissae (whiskers) has been postulated from the presence of pits on the snout of therapsid taxa from the Late Permian,[1] though they are absent in extant mammals. Instead, mammal whiskers extend from a single infraorbital foramen within the soft tissue of the snout, outspreading from the trigeminal nerve. Benoit et al.[12,29] and Muchlinski et al.[30] find that this latter condition developed in the Late Triassic and may be linked to nocturnality.

It has been suggested,[19,31] with evidence ranging from ocular morphology[32] to genomics,[33] that low-light activity (nocturnality, and/or crepuscularity) may have been the predominant activity pattern for ancestral placental mammals. This "nocturnal bottleneck" hypothesis premises that competition with other diurnal vertebrates facilitated a growing dominance of low-light activity patterns amongst early eutherian mammals (Box 2), and Wu et al.[33] suggest that this extended until the Palaeocene.

Due to their generally cooler temperatures, low-light environments are easier for animals to physiologically maintain a Tb consistently above Tas, compared to most diurnal environments.[8,13] Lovegrove[45] highlights the need for a sufficient thermal gradient between Ta and Tb for physiological thermoregulation (Ta < Tb), especially for small-

**Box 1: Synapsid evolution**

Mammals are the living representatives of the synapsids, one of the three major lineages of "amniote" terrestrial vertebrate animals (groups that lay their eggs on land). Distinguished from diapsids (the group comprising living reptiles and birds), and anapsids (comprising several extinct clades and potentially turtles), by a single opening in the skull behind the eye, synapsids have an evolutionary history dating back to the Carboniferous period (Pennsylvanian, approximately 323 million years ago; herein Ma).

The first major group of synapsids is known as the pelycosaurs, typified by the sail-backed *Dimetrodon* (Figure 1). This group retained many primitive features shared by contemporaneous terrestrial vertebrates, with sprawling gaits, slow growth, and ectothermic physiology. Although now considered a paraphyletic "grade" of associated taxa, as opposed to a monophyletic clade, pelycosaurs were the dominant synapsids for the first 40 million years of their history, eventually being superseded by the therapsids during the early Permian.

The therapsids are the first synapsid clade to show significant modifications of the body plan, and the earliest appearances of many features seen as typically mammalian traits (Figure 1). The post-cranial anatomy saw major modifications allowing a greater range of motion. Therapsids radiated during the early-mid Permian, diversifying into a wide variety of ecologies, with the carnivorous theriodont clade the dominant predators of this period. This radiation was halted by the End Permian Mass Extinction Event (EPME), which drastically effected therapsid diversity. Once thriving groups were reduced in diversity, abundance and body size, and others became completely extinct.

One group of therapsids, the cynodonts, diversified into several empty niches following the EPME. Cynodonts radiated through the Triassic, and underwent modifications associated with a comparatively developed physiology (discussed in this review). The Late Triassic saw the evolution of the most derived cynodonts, the probainognathia. This clade underwent some of the most fundamental changes related to physiology amongst non-mammaliaform synapsids, with developments in brain size and shape,[11] the first suggested appearance of sensory vibrissae[12] (whiskers), and significant changes to nasal anatomy permitting greater control of air flow.[13] The miniaturisation of derived cynodonts through this period is also concentrated amongst the probainognathians, correlating with these developments and the exploration of insectivorous niches and specialised herbivory.

The mammaliaforms developed from a probainognathian ancestor during the late Triassic. This group comprised small-bodied nocturnal/low light taxa that radiated during the Late Triassic–Mid Jurassic and considerably expanded their repertoire of "mammalian" features (Figure 1). Mammaliaforms are the synapsid taxa most closely related to crown group mammals—those that are descended from the most recent common ancestor (MRCA) of the three lineages of living mammals-monotremes, marsupials and placentals. The early divergence of monotremes from marsupials and placentals currently places the MRCA of living mammals at approximately 166 Ma.

All living mammals are united in the possession of mammary glands, a fur pelage, pinnae (external ears), and developed "endothermic" thermophysiology and large encephalisation quotients (the ratio of brain volume to body mass). The monotremes are the earliest diverging group, and the most distinctive. The two living genera, platypus and echidna, are characterised by their oviparity (egg-laying), lack of nipples, lack of adult teeth, and low metabolic rates compared to other mammals. While it is tempting to use these animals as a model for more primitive fossil mammals, recent palaeontological and genetic studies show a more complex evolutionary history.[14]

Marsupials and placentals are the living representatives of a monophyletic group, Theria. The earliest fossil therian is the Late Jurassic *Juramaia*, and all subsequent taxa are linked by their possession of specialised tribosphenic molar teeth. Fossil therians are also united by several modifications to the postcranial skeleton, and living therians are viviparous (live birth). Therian mammals underwent a dramatic radiation after the End Cretaceous Mass Extinction 66 Ma, exploiting the wide variety of niches left open by the extinction of non-avian dinosaurs and new niches created by climate change, becoming the only mammalian group occupying almost the entire earth, and diversifying into every major climatic zone seen today.

bodied taxa with small thermal gradients between their Tb and the wet bulb temperature of surrounding air. As wet bulb temperature approaches an animals skin temperature, heat dissipation becomes increasingly difficult which can eventually lead to hyperthermia.[45] This is a particular problem in warm, humid diurnal environments.[45]

However, while nocturnal environments provide less risk of hyperthermia and overheating, continued exposure to such environments may risk hypothermia and heat loss. Heterothermy consists of bouts of homeothermy interspersed with torpor (and/or hibernation) during environmentally unfavourable periods and is experienced by many small nocturnal mammals[45] (alongside large diurnal taxa) with high capacity for losing body heat during nocturnal activity. This buffers heterotherms against daily changes in Tas and allows them to retain

lower average metabolic rates through the diurnal/annual cycle by concentrating activity in favourable periods, and conserving energy during unfavourable periods.[9] Several studies[13,45–48] have used the phylogenetic placement of heterothermy to suggest it is also ancestral for crown mammals, though may also have been secondarily acquired amongst endothermic clades allowing increased energy or water conservation.[48,49]

Independent lines of evidence for both low-light activity and heterothermy in taxa from derived cynodonts to early mammals have been used to infer a lifestyle of nocturnal or crepuscular activity, with low Tbs and intermediate BMRs between extant ectotherms and homeotherms, bolstered by regular periods of torpor/hibernation.[45–48] This hypothesis in-turn requires (a) the presence
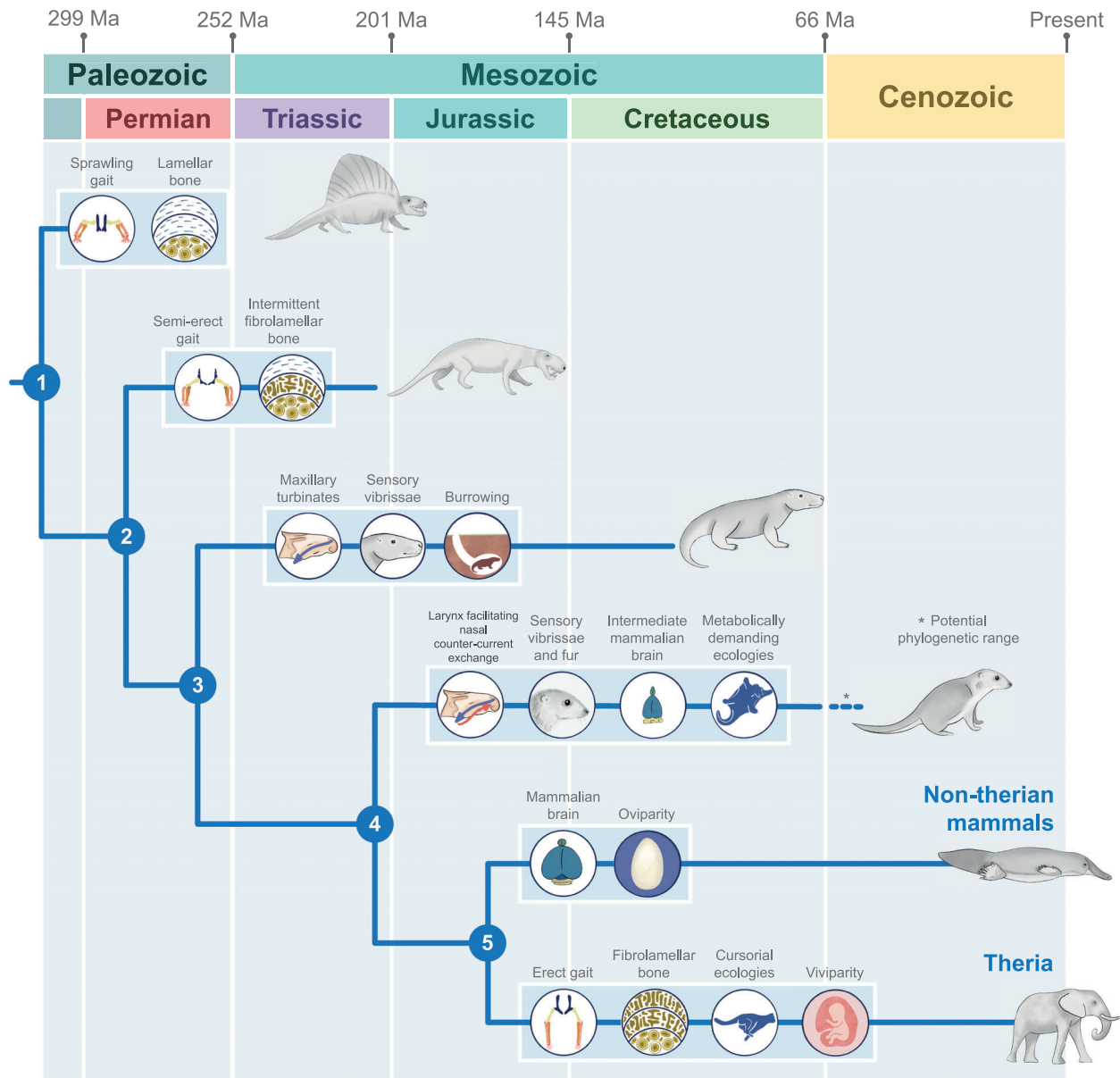
**FIGURE 1** Time-scaled cladogram highlighting the first appearances of a subset of the characters interpreted as evidence for physiological evolution across the synapsid phylogeny. Numbered nodes represent the primary synapsid groups (Box 1). 1, Pelycosauria (paraphyletic); 2, Therapsida; 3, Cynodontia; 4, Mammaliaformes; 5, Mammalia; 6, Theria. Length of terminal branches represent the known fossil records of each group. Figure produced by Nuria Melisa Morales-Garcia

of a fur pelage for insulation, and (b) the delayed rise of homeothermic BMR amongst crown mammals. Evidence of a full fur pelage is first preserved in the Middle Jurassic docodont Castorocauda[22] (although see[50] for interpretation of hair-like structures in Upper Permian coprolites), suggesting an origin outside crown Mammalia amongst Middle Jurassic mammaliaforms. However, the requirement that development of sustained diurnal homeothermy took place within crown mammals conflicts with hypotheses of endothermic metabolic rates and even sustained homeothermy in pre-mammalian synapsids, based on a range of fossil[1,18,51,52] and molecular[6] evidence.

Histological techniques have sought to provide more direct evidence of metabolic processes in fossils. Extant endotherms show a pronounced difference in long-bone microstructure compared to

ectotherms, reflecting their elevated growth rates and potentially their basal/RMRs.[1,53] Ectotherm long-bones are dominated by "lamellar" bone, deposited in orderly concentric layers. Endotherms typically show "fibrolamellar" bone, consisting of rapidly deposited and chaotically organised woven-fibred bone.[1] Fibrolamellar bone has been identified intermittently amongst synapsids as early as the pelycosaur *Ophiacodon*[53] and is sporadically found in therapsids and early cynodonts, suggesting comparatively "flexible" growth strategies relative to extant mammals,[54] and similar to extant crocodilians.[55] While several late Triassic cynodonts show more "mammalian" bone growth patterns, others exhibit lamellar bone even in early ontogeny, suggesting that even the most derived cynodonts still displayed a wide variety of growth strategies and rates.[23]

**Box 2: Revisiting the nocturnal bottleneck**

In an influential study of the visual systems of extant mammals, Walls[34] concluded that early eutherian mammals were restricted to nocturnal activity patterns to avoid diurnal predation by dinosaurs, coining the term "nocturnal bottleneck". This hypothesis has been foundational to a wide range of further studies, and a diversity of palaeontological, genetic and physiological evidence supports the predominance of nocturnal activity amongst Mesozoic mammals (see Gerkema et al. [35] for a review).

One approach to studying visual systems is eye shape analysis. Hall et al.[32] measured cornea size amongst extant vertebrates, as nocturnal taxa typically have relatively large corneas for increased visual sensitivity. They conclude that mammals were initially nocturnal, as most extant mammals have relative cornea sizes comparable to nocturnal birds and lizards. Even with a subsequent mammalian change to a diurnal lifestyle, they suggest that there is not sufficient selective pressure for change, as the iris cannot increase the pupil beyond the size of the cornea in response to low light levels. Angielczyk and Schmitz[36] aimed to establish a date for the origin of the "nocturnal bottleneck", by measuring the scleral ring and orbit dimensions in 24 fossil synapsids ancestral to mammals. They conclude that non-diurnal activity patterns are far older than the origin of mammals, and that nocturnality possibly evolved several times independently through the synapsid lineage.

Another approach has been to focus on the development of ocular light sensitivity amongst early mammals. Kim et al. [37] investigated photopigments in the eye; where cones are sensitive to bright-light environments and enable colour vision, and rods function best under dim-light conditions. The study concluded that rods emerged early on as the dominant photoreceptor in the mammalian eye, during a nocturnal phase early in mammalian evolution. Gerkema et al. [35] also posited that the relative scarcity of ocular sensitivity to ultraviolet (UV) light amongst living mammals suggests a dominance of low light lifestyles earlier in their evolution, reducing exposure to UV radiation. However, a study by Douglas and Jeffery[38] examined the lenses of a wide range of mammals, diurnal and nocturnal, and found a wide diversity in UV transmission and visual acuity. This cautions that nocturnality should be considered in context.

Could a crepuscular or "twilight-bottleneck" offer a better explanation as the predominant activity pattern of the earliest mammals and mammaliaforms? Davies et al. [39] analysed opsin-based photopigments and argued that, as mammalian ancestors extended their behaviour towards dusk (and dawn) day phases, their visual system would be subjected to dim-light conditions resulting in the activation of both cone and rod-based vision. This twilight shift in activity would synchronise feeding with the maximal activity of their prey (e.g., insects, annelids) and avoid predation from larger, diurnal archosaurs. Although the vision of most extant mammals is rod-dominant, they typically possess two cone classes with maxima at opposite ends of the light spectrum. Under purely nocturnal conditions, most (if not all) cone opsin genes would be expected to be lost, but a supposed "nocturnal-bottleneck" did not have this effect. The fossorial ecology predicted for some mammaliaforms may have also promoted the loss of cone opsin genes-we need to consider whether cone loss during synapsid history could also be related to this lifestyle, and not only to nocturnal and/or crepuscular activity.

A tenet of the original "nocturnal bottleneck" hypothesis[14] is the assumption that ectothermic, and therefore diurnal, dinosaurs were preying upon eutherian Mesozoic mammals. The modern interpretation of archosaur physiology undermines this (see [1]), and niche partitioning according to orbit size[40] and scleral ring and endosseous cochlear duct of the bony labyrinth[41] suggests many terrestrial archosaurian predators, including dinosaurs, were partially or fully nocturnal. While the body of evidence points to Mesozoic mammals adopting a crepuscular, or even nocturnal, lifestyle, and potentially spending time in burrows or rock crannies, this is unlikely to have been driven solely by the need to escape archosaur predators.

Another explanatory factor to consider is the expanding availability of insect food resources and dietary niches. The end Permian mass extinction (EPME) marks a division of insect history into two evolutionary faunas[42]. The earlier Palaeozoic fauna comprised many wingless insects, whereas the replacing Mesozoic fauna has a wide range of derived, principally flying clades (e.g., crickets, cockroaches, beetles, and moths). The clade Holometabola, comprising most living insect species, experienced high diversification in the Middle-Late Triassic, potentially as they were more resilient to Early Triassic environmental disturbances, with a protective pupal stage.[43] Within this group, lepidoptera (moths and butterflies) evolved their tube-like proboscis in the Middle Triassic (∼241 Ma), leading to rapid diversification.[44] This diversity of insects would have provided abundant prey for Mesozoic insectivores during low-light periods of the diurnal cycle.

## Evidence and hypotheses for increased activity levels and MMR

A range of evidence in pre-mammalian synapsids and living mammals[56] has been used to suggest that elevated activity levels and MMR were the primary driver for endothermic evolution, particularly morphological advances suggestive of sustained aerobic activity. There is an unquestionable change in posture in early synapsids, from the sprawling gait of Early Permian pelycosaur-grade taxa to the posture of Permian-Triassic therapsids that trended closer towards the parasagittal gait of extant mammals[18,57] (Figure 1). Therapsids could raise their body further above the ground, and modifications

to lumbar vertebrae reduced lateral axial undulation, which restricts breathing while running (see Benton[1] for discussion of this "Carrier's constraint"). This is commonly suggested as reflecting selection for increased aerobic capacity/scope. However, extant crocodiles and varanid reptiles have also developed a more upright posture than other ectothermic reptiles and overcome Carrier's constraint in novel ways, with an analogous diaphragmaticus muscle or gular pumping (respectively) to enhance ventilation during exercise.[58]

A morphological characteristic commonly associated with increased aerobic capacity (although also beneficial for increased BMR) is the secondary palate[1], already developed in the Early Triassic *Thrinaxodon*.[59] This convergently evolved in mammals, birds and crocodiles and allows continuous airflow through the nasal cavity while eating. Extant endotherms also possess nasal turbinates, a complex system of scrolled bones within their nasal passages that stabilise the temperature and humidity of ventilated air. Non-mammaliaform synapsids retained a cartilaginous nasal capsule,[60] and Hillenius[51,61] provided the first evidence of fossilised ridges in a Late Permian therapsid, interpreted as supporting cartilaginous precursors to mammalian maxillary turbinates. However, the first unequivocal ossified nasal turbinals are found in Late Jurassic docodont mammaliaforms,[62] potentially placing their origin in the Middle Jurassic outside crown Mammalia.

Crompton et al.[13] employed micro-CT imaging to conclude that cynodonts and mammaliaforms possessed cartilaginous maxillary nasal turbinates, but questioned whether they played the same role as bony turbinates in extant mammals. Mammals can regulate the temperature of respired air by positioning the larynx in an intra-narial position to create bidirectional airflow across the maxillary turbinates, serving to regulate Tb and conserve respired water. Early cynodonts lacked the musculature to achieve this but could potentially reduce Tb by cooling blood through the turbinates and "dumping" warmer expired air through the mouth (akin to panting during aerobically intense exercise and/or hot conditions in extant mammals and varanid reptiles), as well as achieving counter-current exchange through the nose while at rest if the mouth remained shut. Musculature changes, and the evolution of the pterygoid hamulus, enabled later cynodonts and mammaliaforms to position the larynx and maintain a counter-current through the turbinates,[13] allowing greater control of Tb and hydration both during rest (BMR) and prolonged aerobically intense activity (MMR) (Figure 1). Although these combined modifications of the nasal system may have allowed for moderate increases in BMR and MMR over ancestral synapsid rates, they most likely are not associated with metabolic rates in the range of modern mammals until the Middle-Late Jurassic origin of fully ossified turbinates.

Palaeohistological studies also suggest increased aerobic capacity amongst derived cynodonts, by estimating red blood cell (RBC) size from long-bone microvasculature. Extant endotherms have smaller RBCs than ectotherms, allowing faster oxygen uptake during aerobic activity.[1] Huttenlocker and Farmer[63] concluded that RBC widths in Late Permian-Early Triassic synapsids indicate an increasingly active lifestyle. However, they also caution that, alongside morphological adaptations for burrowing and the widespread occurrence of pre-

served burrow systems,[64,65] this may be instead indicative of adaption to extreme hypoxic environments in this interval, dominated by the End-Permian Mass Extinction (Figure 1).

Most recently, we used a combination of X-ray imaging techniques to analyse novel physiological metrics in preserved features of the teeth and femora of the earliest mammaliaforms *Morganucodon* and *Kuehneotherium* that offer a link to measurable aspects of physiology, such as BMR and MMR (Box 3). Our results suggest that these mammaliaforms had subendothermic BMR (i.e., within the range of extant reptiles), but MMR was intermediate between terrestrial extant mammals and reptiles of comparable size, though closer to reptiles.[10]

In summary, the application of novel imaging and analysis techniques has provided new evidence and more nuance to interpretations of the physiologies of fossil synapsids. It is crucial that the implications of these developments are accounted for when interpreting their long-term physiological evolution (Box 4).

## PUTTING IT ALL IN ORDER: A TIMELINE OF EVIDENCE AND HYPOTHESES FOR SYNAPSID PHYSIOLOGICAL EVOLUTION

We have reviewed a wide range of evidence suggested by prior authors as indicative of the selective pressures, origins, patterns, and pace of synapsid physiological evolution. These present a complex, often-contradictory chronology of when and where "endothermy" was acquired in the fossil record (Figure 1). For clarity, herein we refer to the attainment of endothermy in the synapsid fossil record as the first synapsid clade to acquire both a BMR and MMR within the current range of mammalian taxa. It is also likely that the effects of current traits, and the selective pressures acting upon them, have varied over evolutionary time and so the current effect of a physiological trait does not aetiologically equate to past fitness. Seebacher[98] provides a useful warning against aetiological causal oversimplification (i.e., 'The Single Cause Fallacy'[99]) when discussing endothermic evolution, and a reminder that the current consequences of endothermy (i.e., increased thermoregulation and increased aerobic activity) should not be expected to be the sole explanation for its entire evolution. Novel genotypes and phenotypes may have been selected for under particular sets of environmental conditions, at particular points during evolution, but it is at odds with basic evolutionary processes that this leads to an evolutionary trajectory with a single linear outcome. Hence, when comparing hypotheses for the causes and evolutionary regimes for endothermic evolution, it is important to note that no single hypothesis is likely to model the entirety of synapsid physiological evolution, which probably followed patterns consistent with different hypotheses at discrete times, and with respect to phylogeny.

These are important points to consider when reviewing the evidence for synapsid physiological evolution. When alternative implications of each line of evidence are reviewed in a chronology accounting for broader biological and environmental change, a series of long-term selective pressures and patterns can be suggested, that place evidence into a robust macro-evolutionary hypothesis. This offers a

**Box 3: New tools for studying fossil mammal physiology**

In Newham et al. (2020), our research team published the first cementochronological data for non-mammalian synapsids.[10] Cementum, the tissue anchoring mammal tooth roots to the gum, is unique amongst mammalian hard tissues as its growth is continuous through life and it is not resorbed. This offers a complete record of life history, with each year of life marked by one thick "fast-growth", and one thin "slow-growth" increment, reflecting seasonal changes in growth rate. Cementochronology has been used for decades to estimate lifespans of living mammals, by counting increments in thin-section.[66,67] Synchrotron X-ray tomography has been used to non-destructively count increments and explore life history in a variety of species,[68,69] including fossil mammaliaforms.[10] The circum-annual periodicity of cementum increments was confirmed in our mammaliaform sample by comparing the cementum counts to those of lines of arrested growth (LAGs) in dentary bones. LAGs are known to be annually deposited in living mammals and reptiles[70] and are frequently used to study longevity and growth in fossil clades (e.g., Sanchez et al.[71]).

We found unexpectedly long maximum lifespans in the shrew-sized, 200-million-year-old Early Jurassic mammaliaforms *Morganucodon* and *Kuehneotherium*-14 and 9 years respectively. The maximum lifespan of an animal has been used to infer aspects of their metabolic and physiological life histories, following the longstanding finding that maximum lifespan increases with body mass, and that mass-specific metabolic rate decreases with body size amongst living vertebrate lineages.[5,10] The "rate-of-living" theory of ageing[72] states that the production of harmful free-radicals, as a by-product of normal aerobic respiration, results in the accumulation of damage to cells and the processes of oxidative stress and "ageing". Therefore, an increased metabolic rate serves to increase the rate of accumulation of harmful reactive oxygen species (ROS), increasing the rate of ageing and decreasing lifespan.[73] The most recent advance in rate-of-living theory, the "membrane pacemaker hypothesis", accounts for several caveats of the theory. These include a lack of direct negative effect on lifespan from increased voluntary exercise,[74,75] and specific clades that show a significant departure from the wider trends between maximum lifespan, body mass and metabolic rate seen in their respective broader clades[76] (e.g., Chiroptera, bats, within Mammalia[77]). The higher proportion of highly polyunsaturated acyl chains (e.g., docosahexaenoic acid) in the membranes of mammals and birds compared to non-avian reptiles, and small mammals and birds compared to larger taxa, explains their higher metabolic rate, more rapid ageing and shorter maximum lifespans.[78] This hypothesis also allows the cell membrane composition of certain clades to explain their exceptional relationship to this trend.[79–81]

The membrane pacemaker theory of ageing provided a mechanistic framework for inferring the metabolic potential of our mammaliaforms from their maximum (wild) lifespans. We regressed maximum wild lifespan against BMR/RMR in separate samples of extant terrestrial mammals and reptiles, to estimate both a mammalian BMR and reptilian RMR for our mammaliaforms. Marine and flying/gliding taxa were omitted from both samples due to their known exceptions to the relationships between these factors[76,77,81] (see above). These values were significantly lower than those of comparably sized mammals, but fall within the reptile range. This suggests the earliest mammaliaforms had not attained basal metabolic rates within the range of endothermic extant mammals.

We also used micro-CT to measure the size of nutrient foramina in femoral bones of *Morganucodon* to estimate its blood flow index.[10] The blood flow index represents the maximum blood flow requirements of internal bone cells for remodelling during and after activity,[82,83] and is around ten times higher in mammals compared to reptiles, significantly correlating with their increased MMR.[84] It is likely that the increased size of the nutrient foramina[10] and reduced size of red blood cells[63] in mammals are both adaptive features for providing increased oxygenation for bone cells as well as other cells, to meet the increased demands for limb bone remodelling and repair due to their more active lifestyles made possible with increased maximum metabolic rates. We measured foramina area for *Morganucodon* using micro-CT to overcome the potential obscuring of foramina due to sediment infilling and physical diagenesis-while diagenesis can alter pore dimensions, the exceptional preservation of tooth and bone histological features indicated that foramina had been proportionally well preserved. We calculated the blood flow index $Q_i$ from summed foraminal area following[84] by assuming circularity of this area, deriving the radius, and using the formula $Q_i = r^4/L$ where r is the radius of the effective summed foraminal area and $L$ femur length. This blood flow index was then compared with published and new data for extant mammals and reptiles. No suitable femoral specimens of *Kuehenotherium* are known, so it was not included in this analysis. Our measured foramina areas, and resultant blood flow index estimates, for *Morganucodon* suggest that its MMR was intermediate between terrestrial extant mammals and reptiles of comparable size, though closer to reptiles.[10,84] We concluded that, while elevated above extant ectothermic reptiles, the earliest mammaliaforms had not developed MMR to the levels of living endothermic mammals.

framework for breaking down the long-term evolutionary trajectory into more discrete temporal phases consisting of a portion of the synapsid phylogeny encountering distinct environmental and ecological pressures, and developing specific features that can be related to adaptation to these pressures. Phases additionally offer an explanation for the apparently complex evolution through time and across the phylogeny of many of the characters linked to mammalian endothermy,[10] with characteristics now forming complex physiological systems seem-

**Box 4: Physiology-linked characters at the root of the mammaliaform phylogeny**

*Morganucodon* is one of the earliest mammaliaforms[85] and had evolved a suite of characteristics considered definitive for mammals, including determinate growth,[86] diphyodonty[87] and precise occlusion,[88] and the first evidence of the "mammalian" jaw joint comprising the dentary and squamosal bones.[89] All of these have been linked to assumptions of the evolution of endothermy in these mammaliaforms.

The evolution of the mammalian jaw from the ancestral condition is a well-documented innovation in mammalian evolution,[89] involving reorganisation of the adductor muscles and formation of a novel jaw joint. Using digital models and biomechanical analyses, Lautenschlager et al.[90] suggested that reduction in body size is the primary driver for this jaw joint transformation. These changes to the jaw joint and musculature in mammaliaforms enabled precise mammalian mastication. Precise occlusion, shearing the food and increasing the surface area of the tooth crown able to interact with food, permits more rapid assimilation and has been considered a key innovation in the development of mammalian endothermy.[91] Two other developments, determinate growth and reduction of dental replacement (diphyodonty), are also needed for the development of precise occlusion.[88] Determinate growth, characterised by rapid juvenile growth and truncation of growth at maturity, allows for a reduction in tooth replacement as it limits the time during which teeth of intermediate size are required.[86] This culminates in mammals with a diphyodont condition, with only one replacement of deciduous "milk" teeth by the permanent dentition.[87]

However, although *Morganucodon* had acquired a dentary-squamosal jaw joint, precise occlusion, diphyodonty, and determinate growth, this Early Jurassic insectivore still retained sub-endothermic physiology and lifespan.[10] This suggests that these developments may be better explained by other selective pressures, perhaps associated with dietary specialization and niche partitioning.[10,85] We note that, concomitant to the development of the mammalian jaw joint, was the integration of the reduced ancestral jaw joint bones into the mammalian middle ear, and eventual development of a unique inner ear complex, enabling more sensitive sound detection.[92–94] This would have proven advantageous for detecting insect prey, particularly at night or in low light. The development of precise occlusion will have also benefitted niche expansion and specialisation for predating hard-shelled insect species (see[85]). This expansion of low light insectivory plays a pivotal part in our interpretation of the physiologies of early mammaliaforms.

While related to the weaning of offspring in living mammals, diphyodonty in early (potentially [95]), mammaliaforms may instead be related to fundamental changes in tooth attachment, as interpreted by LeBlanc et al.[94] and suggested by Calamari et al.[96] LeBlanc et al.[94] used thin-section histology to compare the fossilised dental attachment apparatus of non-mammaliaform synapsids with that of living mammals. They found that, although the major elements of the mammalian tooth attachment system were present in early synapsids, teeth were supported within the mouth by ankylosis; the fusion of tooth roots to the surrounding alveolar bone. The authors hypothesise that the gomphosis (teeth supported by the periodontal ligament) of extant mammals developed by delaying the processes producing dental ankylosis in preceding clades. Diphyodonty may be the result of this deceleration, with the development of gomphosis and cushioning of masticatory loading by the periodontal ligament providing biomechanical advantages to a single set of permanent teeth.

O'Meara and Asher[86] compared the mandibular morphology of extant mammals with the fossil mammaliaform *Morganucodon* and tritylodont *Oligokyphus*, to interpret differences in the somatic growth of the lower jaw linked with tooth replacement. The determinate growth strategy, and single replacement of teeth, in living mammals is reflected by significant changes in mandibular morphology during rapid juvenile growth and replacement of deciduous teeth, followed by nonsignificant change through the rest of life. In contrast, the extended growth patterns of non-avian reptiles show consistent changes in mandibular morphology through life. Their results suggest that the earliest mammaliaforms had begun transitioning from a "reptilian" to a "mammalian" growth strategy, with truncated adult growth correlative with the advent of diphyodonty. However, *Morganucodon* also had less rapid juvenile growth than living mammals, and more flexible somatic growth strategies. This is also reflected in the flexible bone growth patterns seen in histological thin sections of the long bones of several mammaliaforms.[97]

ingly evolving out of lockstep, and independently of each other through the fossil record. We can then invoke processes such as exaptation to explain how such features are co-opted, and assume new roles in the evolution of modern mammalian endothermy, adapted to new pressures. This phenological/episodic approach has already been applied by Lovegrove.[45,100,101] However, in the light of our new evidence of metabolic potential in the earliest mammaliaforms, we must reconsider the evidence (Figure 2).

## Phase 1. Carboniferous-to-mid Permian: Terrestrial niche expansion

The anatomy, morphology, and histology of the earliest synapsids of the late-Carboniferous-early Permian suggest that their physiological potential had not developed significantly beyond extant ectotherms.[102,103] From the middle Permian, therapsid taxa display anatomical[8,104] and histological[63] developments suggesting that
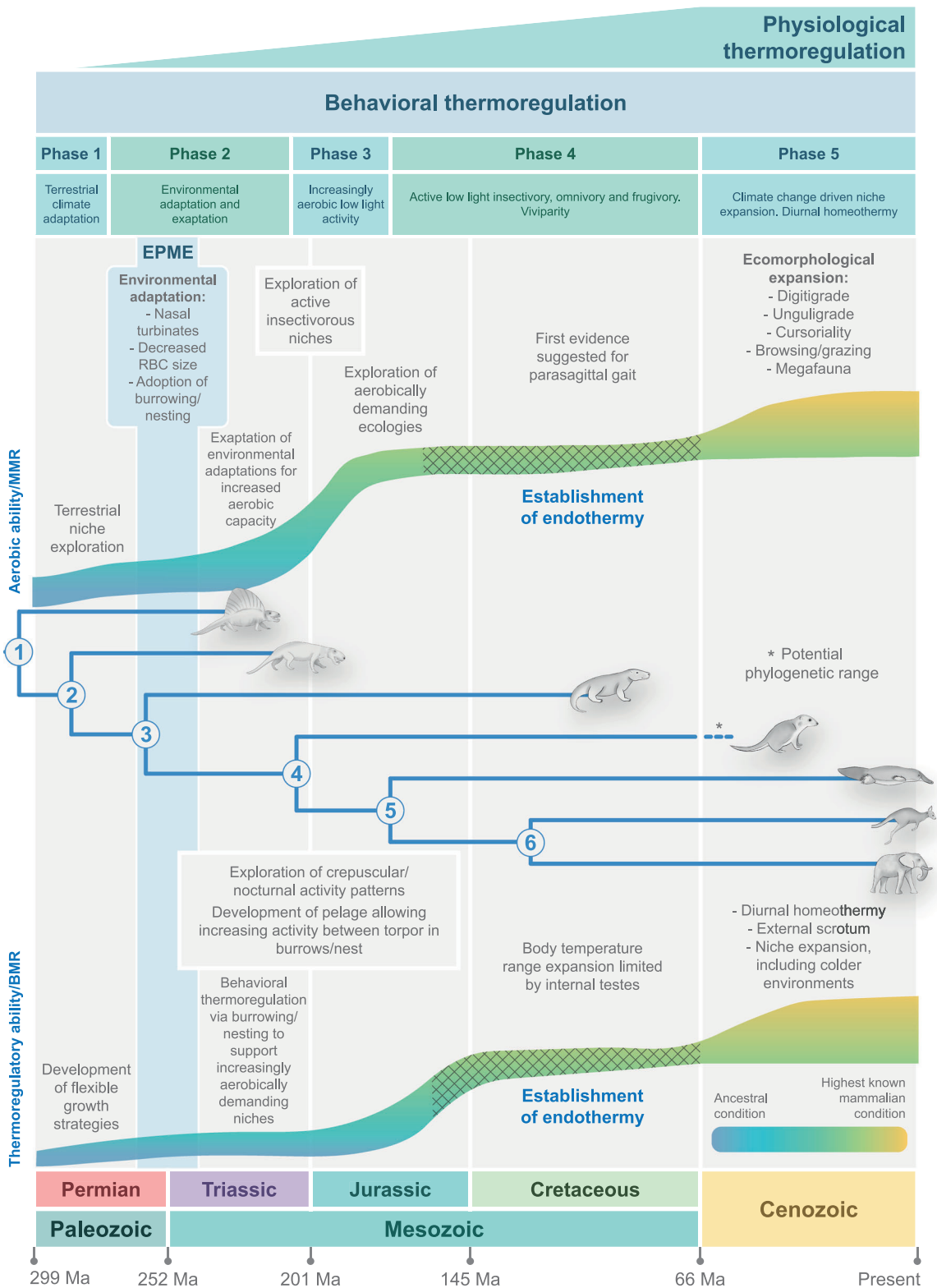
**FIGURE 2** Chronological summary of our interpretation of synapsid physiological evolution, split into five primary phases through time. MMR evolution and BMR evolution are treated separately, with major lines of evidence for the evolution of each factor presented proximal to plots of their respective ranges through time. Numbered nodes represent the primary synapsid groups (Box 1). 1, Pelycosauria (paraphyletic); 2, Therapsida; 3, Cynodontia; 4, Mammaliaformes; 5, Mammalia; 6, Theria. Length of terminal branches represent the known fossil records of each group. Crosshatches represent the time range which hypothesise the establishment of endothermy occurred within. EPME = End Permian Mass Extinction. Figure produced by Nuria Melisa Morales-Garcia

they were capable of more sustained aerobic activity than pelycosaurs. Increasing disparity of forelimb morphologies[105] also suggests significant ecomorphological diversification and niche expansion through the Permian. However, their long bone histology,[54,97,106] and estimates of RBC sizes[63] reveal that they had not yet achieved metabolic rates within the range of extant endotherms.

## Phase 2. mid-Permian-to-Late Triassic: Co-option of features adapted for environmental change

In light of our evidence of non-endothermic BMR and MMR in Early Jurassic mammaliaforms,[10] we reassess the evidence for physiological development amongst earlier synapsid lineages. We suggest that features originally selected for survival in harsh late-Permian-Early Triassic terrestrial environments may have been secondarily co-opted for increased metabolic potential, via exaptation in later taxa. This period, intersected by the End-Permian-Mass-Extinction (EPME), is characterised by increasing atmospheric temperatures and humidity, and a reduced proportion of atmospheric $O_2$[107] (hypoxia). Hypoxia is known to increase respiratory rates via increased breathing rates in extant tetrapods, which in-turn increases the risk of water loss and disruption of heat maintenance.[13] Studies of extant fossorial mammals also suggest that reduced RBC size is also an adaptation for maximising oxygen uptake in hypoxic or low oxygen conditions.[63] Hence, evidence interpreted as suggestive of increased aerobic potential and BMR in synapsids during this period, including reduced RBC size[63] and early evolution of (cartilaginous) maxillary turbinates,[13,51] are equally consistent with adaptation to climatic trends. Evidence for burrowing also suggests that behavioural thermoregulation was prevalent.[108] Large-scale study of synapsid burrow-casts from the Mid Triassic Tarjados formation of Argentina and comparison to those of extant tetrapods by Krapovickas et al.[108] suggest that the fossil burrows were created in strongly seasonal, arid to semi-arid environments, and at sufficient depths to minimise diurnal temperature changes within the burrows to convey a consistent burrow temperature. The near vertical morphology of many burrows is also understood to convey a thermoregulative enhancement in extant analogues.

Contradictory patterns of flexible bone-growth strategies found in histological studies cannot ascertain whether this behavioural thermoregulation appeared prior, or complementary, to physiological thermoregulation.[23,54] However, without evidence for fur and/or the potential adaptations for nocturnal activity found in later cynodonts and mammaliaforms, we cannot assume BMR and physiological thermoregulation within the range of extant mammals.

However, it must be noted that, while the above histological (reduced RBC size) and morphological features (development of maxillary nasal turbinates) may have originated as environmental adaptations, their lack of development in coeval ectothermic clades that survived the same conditions, and convergent appearance in unrelated endothermic clades, at-least underscores their potential for physiological development regardless of their original purpose. Later in the Trias-

sic, some cynodonts developed features indicative of further increased aerobic activity and MMRs. These include continued reduction of RBC sizes[63] outside of the hypoxic environments of the End Permian-Early Triassic, modifications to the girdles and vertebral column allowing further agility and aerobically intensive activity,[57] and the development of more complex counter-current air exchange during exercise through maxillary turbinates.[13] While the functional correlation between MMR and BMR amongst living vertebrates suggest that this was not in the absence of BMR development, our results[10] alongside continued appearance of slow growth, "reptilian" bone structures amongst the most derived cynodonts,[23] suggests that MMR outpaced BMR development through this period.

## Phase 3. Late Triassic-early Jurassic: Nocturnality, miniaturisation and the rise of mammals

A delayed macro-evolutionary increase in BMR, relative to MMR, amongst Triassic synapsids requires re-evaluation of two major interpretations of their physiological evolution: (1) their pronounced body size miniaturisation; and (2) their potential exploration of low-light niches. Observing a pronounced reduction in average body size through this period, McNab[109] first suggested that the benefits conveyed by an inertial homeothermy (the indirect maintenance of Tb in large animals due to their surface area/volume ratio) acquired in large Carboniferous-Permian pelycosaurs and therapsids were preserved in smaller Late Triassic-Early Jurassic cynodont and mammaliaform taxa by increasing metabolic heat production to endothermic levels and developing fur. However, as our results[10] cast doubt on the thermoregulatory ability of these taxa, an adaptation for low-light lifestyles is pivotal for reconciling miniaturisation with BMR values below the range of living mammals.

Following our earlier discussion (Section 2.1), low-light periods provide a lower risk of hyperthermia for small-bodied animals compared to diurnal periods of the same environment, particularly in humid tropical-to-sub-tropical environments[45] (although the amplitude of these differences are environmentally dependent). Cooler low-light activity patterns would have also permitted less developed BMRs/RMRs to sustain Tbs above Tas for subendothermic[10] mammaliaform taxa.[110] Miniaturisation amongst synapsids is broadly accepted as a passive process, driven indirectly by the exploitation of new niches and predation of radiating insect clades (Box 2). So, rather than significantly increase their thermoregulative ability,[10] derived cynodonts and mammaliaforms may have undergone selection for increased aerobic capacity to exploit new prey sources in cooler, low-light periods.

However, the low BMR (relative to living mammals) deduced for Early mammaliaforms *Morganucodon* and *Kuehneotherium*[10] suggests that the sustained exposure to cool Tas in low-light environments of extant homeothermic nocturnal mammals was not possible for derived cynodonts and early mammaliaforms without risking hypothermia. Instead, early mammaliaforms may have exploited crepuscular periods (i.e., dawn/dusk) which place less risk of either daytime hyper-

thermia or nocturnal hypothermia (Box 2). Further, like many extant crepuscular vertebrates, and as suggested by the plesiomorphic status of heterothermic activity patterns for crown mammals,[48] bouts of metabolically demanding exercise may have been facilitated by periods of torpor and/or hibernation, most likely in burrows, to preserve Tb against daily fluctuations in Tare.[45,48,100,108] This activity pattern would have facilitated a selection pressure towards increasingly aerobically active insectivory (and the benefits of increased nutritional intake) without necessitating concomitant developments in BMR and thermoregulation. While fur has been found in the exceptionally preserved Middle Jurassic mammaliaform *Castorocauda*,[22] it is unclear whether the earliest mammaliaforms had a full pelage, or "proto-fur" (*sensu* Lovegrove[45]). Regardless, in the absence of an endothermic BMR, heterothermic behavioural thermoregulation may have been necessary for recovering body heat lost during low-light exercise.

Another study suggesting BMR continued to lag behind MMR through this period is the discovery of a clutch of Early Jurassic *Kayentatherium* tritylodont neonates (a long surviving[105] cynodont clade closely related to Mammaliaformes[111]), over twice as numerous as litters of extant mammals.[95] This suggests derived cynodonts were still egg-layers with large clutch sizes like modern reptiles (in comparison to monotremes), and had not developed the complex parental care and investment strategies indicative of extant mammals .[17,21,48] The relatively mature shape of cranial and postcranial elements of the fossilised neonates relative to their (presumed) parent also indicates a consistent rate of growth through ontogeny, compared to the rapid juvenile growth-rates experienced by extant mammals.[95] Hoffman and Rowe[95] suggest that cranial isometry is most notably due to a significantly smaller EQ in *Kayentatherium* neonates, compared to extant mammals.

## Phase 4. Early Jurassic to late cretaceous: A mid Jurassic pulse and establishment of mammalian endothermy

Our interpretation of the patterns of physiological evolution so far leaves the question of when rates of BMR and MMR within the range of living mammals developed. A study of fossilised nasal chambers[47] concluded that Early Jurassic mammaliaforms had a "low" BMR and "elevated" MMR,[47] matching our recent results of ectothermic BMR and MMR intermediate between ectotherms and endotherms[10] and suggesting the attainment of BMRs within the range of living endotherms occurred in a common ancestor of Middle Jurassic multituberculates and crown mammals. The Early-Mid Jurassic has been proposed as an exceptional period for mammalian evolution, including the first definitive evidence of a fur pelage,[22] development of EQs within the range of modern mammals,[27] and the origination of crown mammals[112] (although see[113]). Ecomorphological and dietary diversification was already present in the Early Jurassic,[85] and gathered pace in the Middle Jurassic into metabolically demanding niches[114,115] and increased locomotor range.[116] Rates of Mesozoic

mammalian phenotypic evolution peaked in the Early Jurassic, ahead of Middle Jurassic disparity and diversity peaks[117,118] (though the most abundant and diverse Mesozoic mammal group, the multituberculates, show disparity and diversity peaks in the Late Cretaceous-earliest Palaeocene[119,120]). It has been hypothesised that the radiation of crown mammals was due to the attainment of a "critical mass" of physiological innovations,[118] and points to significant development of physiology towards endothermic levels. The development of BMRs within the range of living mammals and thermoregulatory advantage conveyed by a fur pelage would have also allowed derived mammaliaforms[22] to proliferate into a wider range of low-light activity patterns that only few living ectothermic clades have managed to emulate.

A dissenting opinion[49,101] posits that the full range of modern mammalian endothermy only evolved in the Cenozoic, following a late Cretaceous "basoendothermic" state (Tbs < 34°C), and characterised by an attenuated ectothermy with increased nocturnal metabolic rate.[45,100,101,121] This hypothesis has recently been challenged by a study using phylogenetic comparative methods on data from living mammals, which suggests that the evolution of Tb and BMR were essentially uncoupled in mammalian evolution.[6] This study suggests that while there was no long-term trend in BMR from the Middle Jurassic Most-Recent-Common-Ancestor (MRCA) of modern mammals to the present day, Tb actually decreased on average between Middle Jurassic and present levels. This proposed lack of overall long-term BMR trend within Mammalia does not exclude the possibility of individual clades or species evolving towards particularly high (or low) BMRs, but suggests that the overall direction of BMR evolution was essentially neutral across the whole of Mammalia, excluding the possibility of the aforementioned Late Cretaceous basoendothermic state. Without fossil data, such methods are unable to reconstruct BMR or Tb in taxa prior to the MRCA of modern mammals, but place an upper bound on the timing of endothermic origin.

This evidence from fossil and living mammals suggests that the mid-Jurassic may represent the approximately 30 million year period in which mammaliaforms or crown group mammals attained metabolic rates within the range of living endothermic mammals[10] (Figure 2). It is uncertain however, whether all mammaliaform and crown mammal taxa present coevally with the MRCA, would have attained the complete complement of physiological variables within the range of modern mammals, or whether there would still have been taxa outside of this range.

## Phase 5. The Cenozoic: Diurnal homeothermy and climatic adaptation

While continued discovery and quantitative inference of locomotor abilities[116] have expanded the known ecomorphological range of Mesozoic mammals, they had yet to explore digitigrade or unguligrade morphologies, and retained the plantigrade posture of earlier synapsids. While this posture facilitated the majority of ecologies occupied by Mesozoic mammals, it limited the extent of cursoriality and running

speeds. The rapid radiation of extant mammalian clades immediately following the End-Cretaceous Mass Extinction[122] gave rise to a concomitant exploration of non-plantigrade and large-bodied ecomorphologies.[123,124] These patterns can be both directly and non-directly related to physiological developments amongst Cenozoic mammals.[45,101] Both BMR and MMR correlate significantly with maximum running speed amongst extant mammals, and cursorial taxa have some of the highest mass-specific BMR and MMR values amongst living mammals.[100] The enhanced cursoriality offered by a digitigrade posture overcomes Carrier's constraint to the most significant degree in synapsid evolution, minimising lateral vertebral undulation and enhancing pulmonary ventilation during running. The evolution of external testes amongst Cenozoic mammals may have also allowed mammals to achieve greater Tbs while maintaining an optimal, cooler temperature for spermatogenesis.[45,101] While not precluding high metabolic rates in extant mammals (e.g., elephants have undescended testicles), this may have been a pivotal element in the breaking of the nocturnal bottleneck, the expansion of diurnal, homeothermic physiologies, and particularly the evolution of "supraendothermic" mammals (*sensu* Lovegrove[45]) —those at the tops of the ranges of absolute (i.e., non-mass-corrected) BMR, MMR, Tb, and other physiological indicators.[45]

The finding of a decoupling of BMR and Tb evolution, but a correlation between BMR and Ta evolution across the extant mammal phylogeny[6] also suggests that climate change played a significant role in the evolution of mammalian BMR through the Cenozoic. The Cenozoic represents a period of global cooling,[125] with events corresponding with the adaptive radiation of major extant mammal lineages. Avaria-Llautureo et al.[6] hypothesise that mammals reacted to cooling events by changing their BMRs (increasing BMRs in resource-rich conditions and decreasing them in resource scarce conditions), reflected in the elevated BMRs/MMRs of high latitude small-bodied mammals, compared to those in more temperate climates.[126]

In summary, we here present a novel interpretation of long-term physiological evolution through the entire history of synapsids, accounting for the latest evidence. Contrary to previous hypotheses, we tentatively place the earliest attainment of metabolic rates within the range of modern mammals amongst the early crown mammals of the Middle Jurassic, following the somewhat delayed development of BMR relative to MMR through the Early Jurassic and early Middle Jurassic.

## FUTURE PROSPECTS FOR RESOLVING THE TIMING OF THE KEY STEPS OF MAMMALIAN ENDOTHERMIC EVOLUTION

The evidence presented here suggests that the lag of BMR development with respect to MMR development may have been closed by early crown mammals during the Middle Jurassic, and that these were the first synapsids to achieve a predominantly physiological thermoregulation, elevated Tbs, and metabolic rates within the range of living mammals. However, it remains uncertain whether all Middle Jurassic mammals had attained this state, or whether it rose to dominance amongst later Jurassic or Cretaceous mammals.

Cementum offers a unique tool for examining BMR development,[10,127] and studying the lifespans of fossil groups spanning the Jurassic-Cretaceous will allow interpretation of their physiological status and the pattern and timing of physiological evolution through this interval. Long lifespans in an abundance of taxa will support delayed development of BMR with respect to MMR (which can be further examined with analysis of femoral blood flow in suitable samples[10]). An opposing finding, of short lifespans and high BMRs amongst more derived mammaliaforms and early crown mammals, may instead suggest a significant pulse of physiological evolution through the Early-Mid Jurassic, culminating in the origin of crown mammals with modern mammalian-level BMRs.

Further, as previously discussed (Section 3) it is likely that synapsid physiological evolution was characterised by different models through time and with respect to phylogeny. The Late Jurassic to End Cretaceous was typified by significantly lower rates of mammalian ecomorphological evolution than the preceding Early to Mid-Jurassic[118] and, while being found to inhabit an increasing number of ecological niches, mammals were restricted in several important physiological aspects, including body size and gait.[45,122] This later Mesozoic interval was also governed by relatively stable climates in comparison to climate-change dominated periods before and after.[45] Hence, it is possible that, during this period, physiological evolution was driven by small-scale changes that benefitted both BMR and MMR equally, as opposed to adaptations to significant environmental pressures that concentrated on one factor. This is a crucial tenet of the correlated progression model,[8] and so the use of comparative analyses of cementum and femoral nutrient foramina in mammals from this interval has the potential to test the validity of this model for macroevolution of complex features such as physiology.

One intriguing prospect suggested by the results of Alvaria-Llauturio et al. [6] is that, while no link is found between BMR and Tb evolutionary rates across the whole extant mammal phylogeny, there is a superficially similar pattern between them in the marsupial clade. Analysis of whether a BMR/Tb evolutionary rate link is present in marsupials, alongside estimation of BMR and MMR in the comparatively rich Mesozoic metatherian (marsupial lineage) fossil record[117,122] would be a further interesting avenue of investigation.

Until these lines of research are completed, the available evidence allows us to conclude that an insulative pelage[22] and high Tb[6] facilitated, or were emblematic of, an ability for physiological thermoregulation, and a wealth of aerobically demanding lifestyles demanded developments in aerobic capacity amongst derived mammaliaforms[22] and early crown mammals.

## CONCLUSIONS: THE WHY, HOW, AND WHAT OF MAMMALIAN ENDOTHERMY EVOLUTION

Our essay has sought to balance interpretations of the most up-to-date evidence for physiological evolution amongst synapsids, using the

arguments made by Seebacher[98] against teleological reasoning and aetiological causal oversimplification as a logical framework. We have followed Lovegrove[45,101] in using a phenological approach for dividing physiological macro-evolution into several core phases.

We differ from most previous interpretations through; (a) a reinterpretation of apparent hallmarks of physiology in non-mammalian synapsids; (b) advocacy for a complex, independent pattern of evolution of those hallmarks and other factors closely linked to metabolic rates; and (c) our predicted establishment of endothermy in Middle Jurassic crown mammals. Our interpretations can be directly and effectively tested through the continued study of such hallmarks, more closely linked proxies of MMR/BMR, and especially of fossilised dental cementum, in as wide a range of mammaliaforms and early mammals through time and across the phylogeny as possible.

A distinction of our approach is that the development of aerobic scope, and/or thermoregulation, was not the sole driving force behind features deemed conclusive indicators of fossil physiology, and questions whether enhanced thermoregulatory ability and/or aerobic scope were the primary and consistent selective drivers behind the evolution of the endothermic physiological regime that typifies extant mammals. If each of our phases is summarised in terms of the pace of evolutionary development in either factor, our hypothesis more closely aligns with the aerobic scope hypothesis, due to the apparent lag in thermoregulatory development behind that of aerobic scope in early mammaliaforms. However, our interpretation does not constrain the evolution of "endothermy" to be a turning point along a path towards aerobic capacity and/or thermoregulatory ability. Instead, we view the evolution of the current physiological range in mammals as the present manifestation of responses to discrete periods of environmental pressures and ecological opportunities. This circumvents the potential problems of teleological reasoning and aetiological causal oversimplification, as the functions of particular features associated with physiology in fossil taxa are reflective of their contemporaneous circumstances, rather than positions along a long-term, directional evolutionary process towards modern endothermy.

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## CONFLICT OF INTEREST
The authors declare no conflict of interest.

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