

3) Why are there so few venomous mammals and no birds, whereas there are so many venomous reptiles?

Throughout popular scientific culture, reptiles, particularly snakes and lizards, are notorious for their use of venom in both predation and defensive circumstances; in contrast, the presence of venom in mammals is notably uncommon, and not at all prevalent in birds. The collection of phenotypes observed in each animal class ultimately stems from the process of evolution by natural selection. A close examination of the principles that have guided the evolution of each class can therefore be used to investigate the contrasting abundance of venomous species within them and the two hypotheses surrounding the evolutionary pathways taken by organisms in their respective environments: convergent and divergent evolution.

A useful mechanism via which the evolutionary principles can be explored is by using the concept of the adaptive, or evolutionary, landscape. This was first introduced by Sewall Wright in the early 1930s. His idea was to represent fitness as a function of possible allele combinations, corresponding to specific genotypes and phenotypes.

Since the genome of an organism consists of a vast number of possible allele combinations, graphically depicting this relationship is difficult because there are many contributing dimensions. However, a simpler 3D model is also possible. In this model, the xy plane represents the degree of similarity between possible genotypes, and the z axis indicates fitness. Peaks in the landscape correspond to regions of high fitness, which an entity can ascend by developing certain beneficial traits through evolution by natural selection; valleys depict regions of low fitness. Species are only able to travel upwards, as it is beneficial for the average organism of a species to improve in fitness for survival, and thus species will not cross a valley. Nevertheless, peaks and valleys may shrink and grow over time as

selection pressures shift due to the ever-changing nature of the environment and thus may change the evolutionary pathway of a class. Using this model is useful because it facilitates an intuitive appreciation of how taxonomic groups of organisms evolve over time, and therefore provides a mechanism via which the evolutionary history of the animal classes can be explored.^{1, 2} To connect this to the evolution of venom, it may be useful and

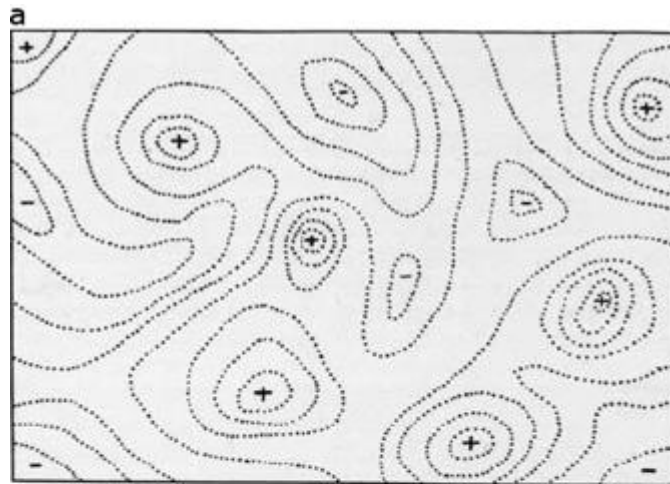


Figure 1 – Wright's original depiction of the adaptive landscape

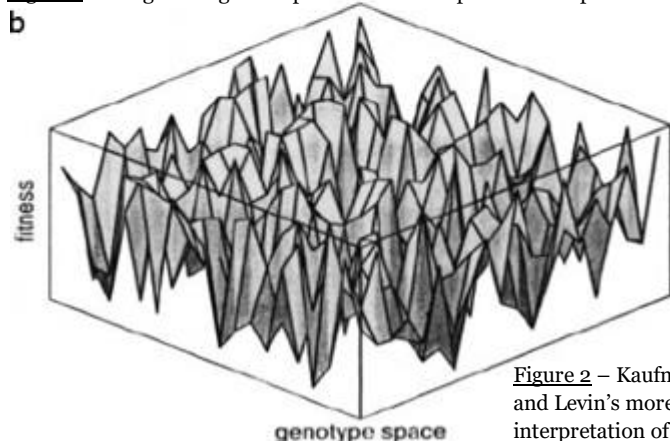


Figure 2 – Kaufman and Levin's more recent interpretation of the adaptive landscape

appropriate to model venom presence as a distinct peak to those of claws and teeth, a feature of many mammals, and the use of flight in birds. From this, it can be deduced that a mammal possessing claws and teeth, for example, would not tend to cross a valley to a different maximum fitness peak and develop venom unless there was a dramatic change in selection pressures which caused the landscape to adapt.

The landscape model can be used to consider why reptiles have more venomous species than mammals and birds. Historically, the evolution of venom in reptiles has been widely disputed and can be categorised into two main hypotheses: divergent and convergent evolution. The argument for divergent evolution, known as the Toxicofera Hypothesis, asserts that all venomous animals are descendants of a singular ancestor which had itself adapted to adopt venomous traits. On the other hand, convergent evolution claims that venom evolved several times in the past.

The Toxicofera Hypothesis was first introduced in 2006 by Fry et al. in the scientific journal, Nature. The research group proposed the existence of a clade of squamates, *Toxicofera*, which translates from Greek to mean ‘those who bear toxins’; this clade is composed of the snakes, iguanians, and anguimorphs. As per their hypothesis, all lineages of this clade

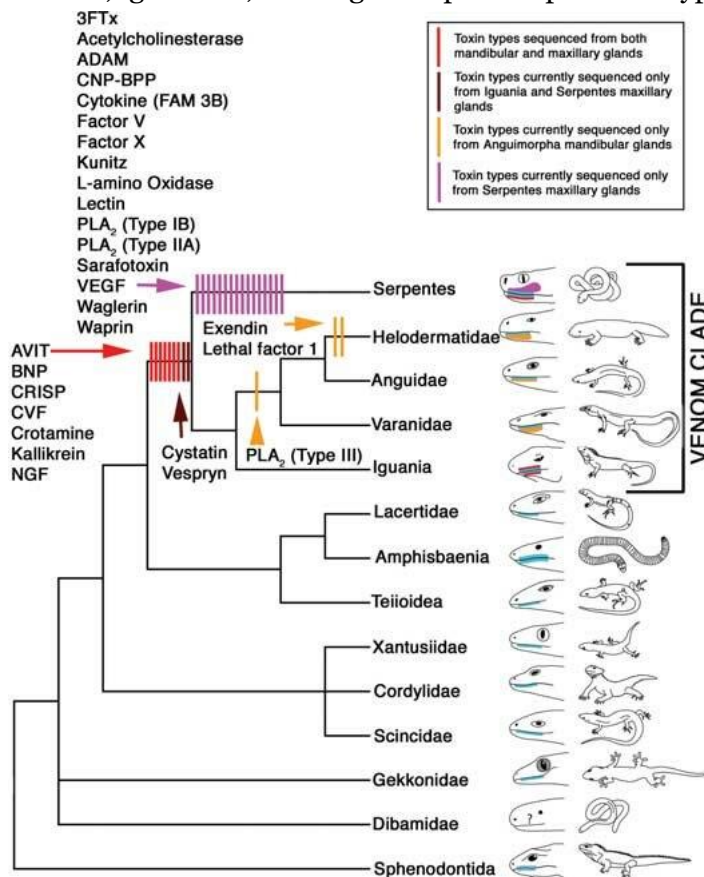


Figure 3 – a phylogenetic tree showing the divergence of the *Toxicofera* clade and associated toxin types

possess ‘uniquely derived mandibular and maxillary glands distinguished by having segregated protein and mucus secreting regions’.³ In their publication, they postulated that the existence of such a clade provided overwhelming evidence for ‘a single, early origin of the venom system in lizards and snakes’, claiming that all venomous reptiles share a common ancestor which existed over 200 million years ago. This conclusion was drawn as a result of the examination of gland complementary-DNA libraries and transcript-based phylogenetic analysis which demonstrated that 9 toxin types are shared between lizards and snakes. Moreover, they proposed that there are 16 basal venom toxin genes that encoded for venom across the *Toxicofera* clade.^{4, 5}

According to the landscape model, the Toxicofera Hypothesis proposes that the common ancestor of venomous reptiles ascended a peak corresponding to the venomous trait, thereby dictating the starting position of all descendants. Most descendants have remained on this peak ever since, diverging in other ways whilst retaining the venomous trait. In contrast,

both mammals and birds had no such common ancestor, and therefore occupied a different starting position on the landscape which did not render them venomous.

Although the Toxicofera Hypothesis was accepted across the scientific community for over a decade, a research team comprised of experts from various different institutions and led by Dr Adam Hargreaves heavily criticised and disproved Fry's proposition in the mid-2000s. They argued that the studies conducted by Fry et al. optimistically attributed the toxic effects of venom to certain proteins found in species of the *Toxicofera* clade, as they were expressed in the glands during venom synthesis and due to their genetic relation to other known toxins. Hargreaves and his team decided to analyse a number of different tissues – 'venom or salivary glands, skin and cloacal scent glands' – in five reptile species and identified DNA transcripts encoding for the same putative venom toxins. They reasoned that it was 'unlikely that the same gene could fulfil toxic and non-toxic (pleiotropic) roles without evidence for alternative splicing to produce a toxic variant... or increased expression levels in the venom gland' and that, if there was indeed a pleiotropic gene, there would be an elevated expression in the venom glands compared to other tissues. Through genetic analysis of the five species, they identified many of these genes in other body tissues which are not involved in venom production or secretion and found that there was 'no evidence of consistently elevated expression level in venom or salivary glands compared to other tissue', thus showing that it was unlikely that these genes had pleiotropic roles. They therefore concluded that the venom toxin genes proposed by Fry et al. are not involved in the production of toxic venom components in the majority of species and were most likely housekeeping or maintenance genes – Fry's hypothesis was likely the result of incomplete tissue sampling. Hence, there is insufficient evidence to suggest the existence of the *Toxicofera* clade and thus it seems unlikely that the presence of venom in reptiles is the result of divergent evolution.⁶

As most recent scientific work suggests, if venom presence emerged in reptiles due to convergent evolution, it prompts the question: why have reptiles discovered the utility of venom more often than mammals and birds? The landscape model can again help to answer this question. The three classes of animals have traced different pathways across the landscape over time, and as such have always had different peaks available to ascend. The ecological niche of the classes has determined the selection pressures each class has faced during its evolutionary history, and therefore influenced the composition of the surrounding landscape. Perhaps less obviously, the phenotypes they have already evolved have also had an influence. This is because of phylogenetic inertia: the principle that the traits already possessed by a group limit, and potentially even promote, the evolution of certain new phenotypes. The pathway taken by a class – in other words, the phenotypes they have already evolved – influences where it already is in the fitness landscape, and therefore where it is able to and is likely to go in the future. For example, it could be considered that the evolution of four limbs in animals led to the formation of accessible peaks associated with the development of hands and feet. The same idea can be applied to the evolution of venom: certain traits already possessed by each class have made it more or less likely for there to be a local and accessible peak corresponding to the venomous phenotype. This discrepancy in the presence of venom across the different taxonomic classes via convergent evolution can therefore be explained by appreciating that the surrounding landscape for the reptile class has often had an accessible peak corresponding to the venomous trait, whereas the local terrain for the majority of mammals and birds has not.

The uses of venom vary across species and are mainly centred around predation and defence. Venomous predators use venom to incapacitate their prey prior to consumption by either 'interfering with nerve action causing paralysis' or 'altering blood and blood vessels causing blood loss and associated shock'.⁷ It is extremely rare for a predator to use venom to directly kill its prey as this would require more venom and is unnecessary; venom itself is energetically expensive to produce and therefore it would not be evolutionary beneficial for fitness if incapacitation is already an effective method of predation. Moreover, reptiles are ectotherms and thus do not expend energy maintaining their internal body temperature as mammals and birds do, meaning they can afford the expense of venom production if it gives them a selective advantage. Perhaps more significantly, reptiles can afford to make enough venom to be used in predation circumstances, whereas the few venomous mammals which exist tend to use venom for defence or feeding.

Compared to reptiles, the presence of venom in mammals is rare, limited to four orders: *Monotremata*, *Eulipotyphla*, *Chiroptera*, and *Primates*. Samuel Papp from the University of Saskatchewan argued that 'Perhaps the unique combination of traits that make up mammals renders venom production cost-prohibitive, or simply unnecessary to be an effective competitor'.⁸ As most mammals themselves possess various other phenotypic traits such as claws and teeth which are effective in both predation and defence, it is not energetically or evolutionary beneficial for them to evolve venomous traits. In fact, most mammals are situated on the adaptive landscape where they do not currently have access to the venomous fitness peak in the surrounding terrain. Birds have also evolved differently, using flight for both evasion of predators and to attack their prey from above. Since flight itself is already energetically expensive and birds require energy to maintain their internal body temperature, they cannot afford the evolutionary cost of venom unless it provides a significant fitness advantage. However, although rare, an example of a venomous mammal is the vampire bat: three species, *Diaemus youngi*, *Desmodus rotundus*, and *Diphylla ecaudata*, employ venom as an anticoagulant to prolong feeding periods. Unlike other species of bat, vampire bats do not have adipose stores and therefore require a constant food supply in order to survive; a constant supply of blood also helps vampire bats to maintain their internal body temperature as they lack insulation from adipose tissue. It is therefore necessary and useful for vampire bats to possess venom, despite having teeth and claws like many other mammals.

Despite the Toxicofera Hypothesis having been the accepted proposal for venom evolution in reptiles, the latest evidence suggests that it was indeed convergent evolution. Being cold-blooded and not possessing other beneficial traits such as teeth and claws or flight, the venom peak on the adaptive landscape was more accessible to reptiles and provided them with a method for both predation and defence. In contrast, the majority of mammals and all birds have no need for venom, as their existing traits already provide them with a selective advantage and are sufficient for their survival. The few venomous mammals that do exist tend to use venom for defensive or feeding purposes when it is necessary and beneficial for them to do so. However, despite the scarcity of venomous mammals and the lack of venomous birds, Wright's model for evolution is indeed adaptive and, although unlikely, there may be a singular selection pressure or a combination thereof that causes a change so radical in the existing landscape that taxonomic classes are forced to gravitate towards other peaks of maximum fitness. It is even possible that there could be an emergence of more venomous mammals and birds, or the absence of venom in reptiles altogether.

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