The Inverse-Krogh principle: all organisms are worthy of study

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Opening Quotations

"It is not necessary to understand things in order to argue about them." Pierre de Beaumarchais

"Comparison is the death of joy." Mark Twain

Abstract

Krogh's principle states: "for such a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied." The downside of picking a question first, then finding an ideal organism on which to study it is it will inevitably leave many organisms neglected. Here, we promote the inverse-Krogh principle: all organisms are worthy of study. Inverse-Krogh and Krogh are not opposites. Rather, the inverse-Krogh principle emphasizes a different starting point for research: start with a biological unit, such as an organism, clade, or specific organism trait, then seek or create tractable research questions. Even the hardest-to-study species have research questions that can be asked of them, such as: Where does it fall within the tree of life? What resources does it need to survive and reproduce? How does it differ from close relatives? Does it have unique adaptations? The Krogh and inverse-Krogh approaches are complementary and many research programs naturally include both. Other considerations for picking a study species include extreme species, species informative for phylogenetic analyses, and the creation of models when a suitable species does not exist. The inverse-Krogh principle also has pitfalls. A scientist that picks the organism first might choose a research question not really suited to the organism, and funding agencies rarely fund organism-centered grant proposals. The inverse-Krogh principle does not call for all organisms to receive the same amount of research attention. As knowledge continues to accumulate, some organisms – models – will inevitably have more known about them than others. Rather, it urges a broader search across organismal diversity to find sources of inspiration for research questions, and the motivation needed to pursue them.

The Krogh principle

Before a biologist can apply their skills, they must pick a question and a study system. The study system can range in level of biological organization from molecules to cell cultures to organisms to ecosystems. In the context of comparative physiology, August Krogh stated that "*for such a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied*" (Krogh 1929 p. 247). Krebs (1975) provided the name "Krogh principle" and listed several examples, including the use of (1) squid giant axons to study nerve conduction (because they are large), (2) pigeon breast muscle to study the tricarboxylic acid cycle (because it has a high rate of respiration in saline solution), (3) the three-spine stickleback to study behavior (because they maintain normal behavior in captivity that is easily observed), and (4) the use of *Drosophila* to study genetics. He concluded by stating that "A general lesson to be learned from these considerations is the importance of looking out for a good experimental material when trying to tackle a specific biological problem" (Krebs 1975, p. 225).

Although Krogh (1929) did not use the word "model" to describe this approach, Krebs (1975) did. In this context, "model" has multiple definitions, which we address more fully below (see also Table 1). As an example of a "Krogh model" (or "Krogh organism" *sensu* Green et al. 2018), if one wants to know how jumping works, a model is an animal good at it, such as a kangaroo or frog (Figure 1). These animals are convenient because they are prone to jump, but also the legs of both are well-developed with large muscles suitable for electrodes (Azizi and Roberts 2010). Moreover, you can get them to sit still on a force plate prior to jumping, thus allowing accurate measurement of ground-reaction forces (Nauwelaerts and Aerts 2006). Measuring how kangaroos and frogs function is comparatively easy, and it is easy to convince them to jump in your experimental setup because jumping is what they do naturally. This approach has obvious merit. Frogs and kangaroos are good models for jumping, but a turtle is unlikely to teach us much about jumping.

Krogh offered his advice regarding convenient animals of choice following a paragraph in which he promoted the idea of conducting physiology on a wide range of organisms. This was a reaction against the narrow focus on a small number of organisms that dominated the physiology of his day (Ankeny and Leonelli 2011; Green et al. 2018). Specifically, he stated that "the general problem of excretion can be solved only when excretory organs are studied *wherever we find them and in all their essential modifications*. Such studies will be sure, moreover, to expand and deepen our insight into the problems of the human kidney and will prove of value also from the narrowest utilitarian point of view" (Krogh 1929, p. 247; emphasis added). Thus, even as Krogh promoted the use of convenient animals of choice, he also suggested that other species deserved study. This latter point receives far less attention when the Krogh principle is invoked, and it is a starting point for the present paper.

In some cases, the Krogh principle has become a simplified catechism, cited without this broader perspective. Gans (1978) paraphrased it as the “principles approach” and lamented that it had become dominant, the “only respectable” and “always critical” approach to adhere to. The more natural-history-driven approach that he favored (and that we espouse here) had fallen victim to an “overwhelming bias.” The downside of picking a question first, then finding an ideal organism is that this approach will inevitably leave many organisms neglected. Consider an organism that is not the best model organism for any particular question. The Krogh approach, rigidly adhered to, subtly implies a pernicious question: why ever study non-model organisms? If every good question in physiology or behavior (or evolution or ecology) would be better answered with a superior model, then most organisms become unworthy of serious inquiry (Figure 1). (In a related example, the use of a *single* animal as a model, the albino laboratory rat, led to the decline of "comparative" psychology (Beach 1950).) Although Krogh was most focused on physiology, here our lens is broader, including questions in ecology, evolution, and behavior.

But this raises a question: What makes a good question good? Research questions often arise from the organisms that are at hand, readily available for study. Some questions are theoretically interesting but impossible to study, because, currently at least, no organism is suitable. For instance, how does an organism with left-handed helical DNA structure perform differently from one with right-handed helical DNA? Life on our planet is based on right-handed DNA (de Rosa et al. 2010), so examples of left-handed DNA do not exist. The courtship displays of sauropod dinosaurs are similarly out of direct reach, although there might be fruitful ways to indirectly address questions about sexual selection in these animals (e.g. Taylor et al. 2011). Although sauropods must have had such behaviors, these dinosaurs are extinct and courtship behavior generally doesn't fossilize. Thus, these two questions are not available for study under the Krogh principle, for no organism is convenient, although as we address below, for certain questions this limit can be circumvented because a suitable organism can be created (Bennett 2003).

Many good questions arise out of consideration of organisms themselves (Bartholomew 1982), which leads us to the inverse-Krogh principle (Figure 1). We use this name somewhat playfully, not to condemn the Krogh principle; its value and power have been proven by the history of science (Dietrich et al. 2020; Lindstedt 2014). Rather, our purpose here is to emphasize that alternatives to the Krogh principle are also valuable and powerful. Introspection on the fundamental question of “What shall I study?” has multiple starting points.

In the initial submission of this manuscript, we used the term "anti-Krogh," which reviewers suggested was counter-productive, and we agreed. A related term we encountered was "reverse-Krogh" (B. Sinclair, pers. comm.). We instead use the term "inverse-Krogh principle." Under the Krogh principle, a question is selected first, then a good organism. The inverse-Krogh principle is the inverse of this: select an organism first, followed by an appropriate question (Figure 1). We note that Kram and Dawson (1998) used "inverse-Krogh principle" to mean "choosing to study a species that has been most appropriate for stimulating new questions rather than providing definitive answers", which is not the same as the definition used here.

The inverse-Krogh principle: all organisms are worthy of study

Carl Gans (1978) titled a paper: "All animals are interesting!" Consistent with this exclamation, the inverse-Krogh principle states that, merely by existing, a species deserves research attention that could inspire or lead to exciting questions (Figure 1). The same argument applies to any other level of biological organization, from cells to ecosystems. This perspective is analogous to George Leigh Mallory's stated reason for wanting to climb Mount Everest: "Because it's there!" (Gillman and Gillman 2001 pp. 221-223). Or, as Barbara McClintock famously described how the importance of having "a feeling for the organism" fueled her day-to-day passion and curiosity for science (Keller 1983), and led to her important insights and achievements in several fields—not least of which included a Nobel prize. David Wake made huge strides in evolutionary and developmental biology by taking a "focal clade" (as opposed to a focal species) approach focusing on plethodontid salamanders (Hanken 2021; Zamudio 2021).

The hypothetico-deductive framework is sometimes presented as if the hypothesis always comes first. But of course, all science has in it the inductive method: observation comes first. All questions (and hypotheses) are rooted in prior observations. Thinking does not occur in an empirical vacuum. Developing a good question can be the hardest step in science, and inspiration may arise from innumerable forms of observation.

What may be studied of any organism? Certainly, some organisms are easier to study than others; as a corollary, some organisms are scientifically better known than others. Extinct species are particularly difficult to study, even indirectly. But at a minimum, some universal questions one may ask of any organism include where does it fall within the tree of life, where does it live, what resources does it need to survive, how does it reproduce, and how does it interact with its environment.

Making a complete list of 'universal' questions is difficult, for it is intrinsically hard to state the limits to scientific inquiry regarding any given organism. It is possible that naming and placement in the tree of life of a previously undescribed taxon is all that science may ever accomplish for the hardest-to-study (or rarest) organisms, such as oceanic bacteria that cannot (yet) be cultured in the lab and are inferred to exist only from sequencing of seawater (Joint et al. 2010), or rare fossils for which we only uncover a single fragment of one individual. It may be difficult to ever learn much of deep sea creatures that live at 1,100 times atmospheric pressure and disintegrate upon reaching the low pressure of the ocean surface, such as snailfish (*Pseudoliparis*), though we suspect Gerringer (2019) would disagree that snailfish are as unknowable as we have just implied.

One can never be sure what the limits to knowledge of a particular species may be; something impossible to study today may become accessible through tomorrow's technological or conceptual breakthrough. Decades ago, telemetry allowed unprecedented access to body temperatures and movements of animals under natural conditions (Cooke et al. 2004; Costa and Sinervo 2004; Hebblewhite and Haydon 2010; Mackay 1964). Even a few years ago, it might have seemed unimaginable that the entire genome of a cave bear could be sequenced out of bones estimated to be 360,000 years old (Barlow et al. 2021), but some cave bear genomics is now possible. Similarly, the colors of dinosaur integuments were long off limits to real scientific inquiry, but thanks to molecular paleontology and new imaging technologies, plus incredible fossil preservation, this question is now an intensive area of scientific discoveries and excitement (Li et al. 2010; McNamara et al. 2021). The precision with which a question may be studied can radically improve via technological and methodological advances, opening up new ways of re-addressing old questions. For example, x-ray radiography and "XROMM" biplanar fluoroscopy led to dramatic improvements in the study of normal and pathological morphology, as well as of the motions of organisms (Brainerd et al. 2010; Gatesy et al. 2010; Pasveer 2006), by allowing visualization of static and dynamic forms and functions of skeletal and other tissues. By definition, limits to knowledge and its acquisition continually shift in ways impossible to anticipate.

This variation in knowledge of any particular species, and source of research question (Krogh vs. inverse-Krogh) is plotted in Figure 2. New species descriptions (lower left) are the starting point, since a newly described species by definition has virtually nothing known about it. In the opposite corner (upper right) are 'standard model' organisms ("the mouse", "the fly", etc.) as used to study 'standard' theoretical questions, such as the biology of cancer. The upper left corner is empty, because the limiting case of an undescribed species with no described biology cannot be a "Krogh model." Whether any research can fall in the extreme lower right corner is debatable. Model species such as *Mus musculus* or *Drosophila melanogaster* have aspects of their natural history which remain poorly known, but whether an investigator could pick a research question on them based *only* on the organism itself, and entirely ignore the literature on these species as they do so, seems unlikely.

Krogh and Inverse-Krogh approaches are complementary

The inverse-Krogh principle we advocate here is not exactly the opposite of the Krogh principle. Instead, the inverse-Krogh principle emphasizes a different starting point for scientific inquiry. Rather than declaring some organisms as useful models for a particular question, as the Krogh principle does, the inverse-Krogh principle emphasizes natural history: observation of organisms as they are. This is the approach of Bartholomew (1982) or Gans (1978) and, we would argue, of Charles Darwin (e.g. Darwin 1851, 1875) (see also Arnold 2003). Darwin's (1859) *On the Origin of Species* was not the result of trying to find a convenient organism to study a biological problem or concept, and he certainly was not testing an *a priori* hypothesis. Rather, this monumental work derived from observing organisms that he happened upon and/or found interesting, and eventually trying to make sense of their diversity of form and habits (Reznick 2009), via inductive, abductive, and hypothetico-deductive means alike (Elliott et al. 2016). Galapagos finches revealed themselves to Darwin as excellent models for the study of adaptation and speciation, and subsequent workers then recognized them as models for these topics and others (e.g. Grant and Grant 2006; Herrel et al. 2005; Loo et al. 2019). Darwin's work on the Galapagos Islands clearly demonstrates the point that consideration of the organism itself, in its natural context, will suggest questions that might be asked of it. We would argue that the inverse-Krogh approach implicitly underlies much descriptive research, including natural history, taxonomy, parts of conservation biology, and construction of phylogenetic trees. Popper (1959) and others have pushed the supremacy of strong inference and the deductive approach. Some even engage in *post-hoc* presentation of research as hypothesis-driven even when that's not how the research project originated (Bartholomew 1982; Kerr 1998), as if exploratory work is "bad" (Rowbottom and Alexander 2012).

Natural history, taxonomy, and other descriptive work sometimes gets a sneer from experimentalists and theoreticians alike: *this work is descriptive* (Hailman 1973). One colleague, in a casual conversation, called this "the eternal war of facts vs. concepts" (or data vs. theory). Science advances on both. We suggest that purely theoretical work with no clear application can be just as subjectively interesting as purely descriptive work with no clear theoretical basis. In the Krogh approach, one starts with a problem that needs solving and searches for an organism on which to collect facts (empirical data) to support, refute or refine the questions involved. In the inverse-Krogh approach, one starts with facts rooted in observations of an organism, and *then searches for questions or invents concepts that can be applied to this organism,* given the initial observations. Both approaches can lead to major advances. Bang was studying horseshoe crab blood circulation when he noticed it coagulated in the presence of bacterial endotoxins (Bang 1956). This initial observation about his organism (inverse-Krogh) became the basis for the *Limulus* amebocyte lysate test (Levin 2019). Important research in conservation biology arose from observation that a species seems to be in decline. For instance, the discovery that DDT induced reproductive failure (e.g. by thinning eggshells) in raptors arose from observation of reproductive failure in raptors (Porter and Wiemeyer 1969). The gene-editing technique CRISPR is arguably the biggest advance in biology in the past decade. Lander (2016) documents that the essential precursor discoveries came from curiosity about salt-marsh microbes and hypothesis-free exploration of bioinformatic datasets - and even that some of these early results were rejected from major journals for being 'too descriptive'.

One of us (CJC) has followed a path that illustrates how research programs may shift over time between Krogh and inverse-Krogh (Figure 3A). Initially we adopted a Krogh approach, using hummingbirds as a model for bird flight, to ask how flight is affected by tails that were greatly elongated by sexual selection (Clark and Dudley 2009). This led to observation of the organism itself. While flying Anna's Hummingbirds (*Calypte anna*) in a wind tunnel, and manipulating their tail-feathers, we observed they have sexually dimorphic tail feathers, but the dimorphic feathers are not long or colorful in a way suggestive of a visual signal. Moreover, males make a distinctive *chirp* during a high-speed dive performed for females; and we found a paper suggesting these dimorphic tail-feathers produce the *chirp* (Rodgers 1940). Rodgers' idea was later disputed (Baptista and Matsui 1979). These observations on the organism itself spurred a set of inverse-Krogh manipulative experiments that unambiguously supported Rodgers' hypothesis: the tail-feathers make the sound (Clark and Feo 2008). Follow-up work expanded the representational scope: related hummingbirds have differently-shaped tail feathers and make different sounds (Feo and Clark 2010). Moreover, other birds have convergently evolved to make sounds with their feathers (Clark and Prum 2015; Darwin 1871 pg. 61-67). One widespread physical mechanism that generates these sounds is aeroelastic flutter (Clark et al. 2013a). Aeroelastic flutter, as an acoustic phenomena specifically, appears to be something that bird feathers, and perhaps no other biological structure, are prone to do (Clark 2021).

Under the Krogh principle, CJC's research approach would have been different. The research question shifted from aerodynamics of elongated tails to acoustic communication in birds. If the research question were framed as: "how do birds communicate acoustically?" then, as most avian acoustic communication is vocal, the Krogh principle suggests studying a bird that is good at singing, such as a mockingbird or zebra finch. The representational scope (sensu Ankeny and Leonelli 2011; Table 1) of this research is, in certain dimensions, somewhat limited. That is, the hummingbird feather work provided a physical acoustic mechanism (flutter) generalizable to birds, but apparently, not bats or insects. Other uncovered patterns do generalize. For instance, mapped on a phylogeny, hummingbird tail-feather sounds evolve as both a continuous character and a genuinely discrete character because how a feather flutters is an emergent property of a dynamical system in which tiny changes in a state variable (e.g. feather width) can have either a small or large effect on flutter, depending on whether a threshold was crossed (Clark et al. 2011; Clark et al. 2018). Many phenotypic characters are emergent properties with a complex physical basis (e.g. locomotor gaits, colors) and so likely also evolve this way (Clark et al. 2018). Moreover there are intriguing patterns of correlated evolution between vocal and nonvocal sounds, such as certain species that make vocalizations with similar acoustic structure to their non-vocal sounds: they produce two sounds that sound the same, despite being produced by different physical mechanisms (Clark and Feo 2010). Such "self mimicry" is not predicted by any current models of complex animal signaling. Finally, this work has led to work on adjacent topics, including how wing hum of hummingbirds and insects is produced (Clark and Mistick 2020) and how quiet flight evolved in owls (Clark et al. 2020), with many possible future directions (Figure 3A).

Another of us (JRH) has had a complex career path that mixes the Krogh and inverse-Krogh principles (Figure 3B). He began with a question about whether a *Tyrannosaurus rex* could run quickly or not, something that was debated in the dinosaur literature (a 7+-ton biped makes a great choice for a study taxon for the limits giant size places on speed; Hutchinson and Garcia 2002). But this soon turned to ask if elephants could run, and how quickly (Hutchinson et al. 2003). Yet these research threads led him to want to place these organisms into evolutionary contexts to understand (for their own sake; and for understanding on a case-by-case basis for their lineage) how their locomotor abilities evolved, and this curiosity prompted questions about form and function. The elephant research thread explored the remarkable foot structure of proboscideans, and serendipitously realized that (1) elephants had very remarkable false "sixth toes" akin to the panda's "thumbs," which they use to support their fatty footpads, and (2) fossils revealed something about the early origin and evolution of these giant sesamoid bone structures and their relationship to foot posture, body size, and terrestriality in early elephants (Hutchinson et al. 2011). Thus, the elephant research turned more to an inverse-Krogh perspective, by following organism-derived observations that inspired the most interesting questions. This research on how animals on land cope with the extreme constraints of supporting themselves against gravity searches both for generalities and unique patterns in lineages that have evolved gigantism on land via an evolutionary biomechanics approach, which integrates Krogh and inverse-Krogh approaches (Hutchinson 2021).

Improbable traits

A thesis of this paper is that the Krogh principle will tend to leave some species under-studied. A corollary is the Krogh principle will also tend to leave certain types of traits un-studied. By finding organisms that fit research questions, the Krogh principle steers research away from the study of traits that are not predicted by pre-existing empirical knowledge or theory. These are improbable traits. As Dawkins (1979) put it: "If spider webs did not exist, anybody who postulated them might well provoke scornful skepticism. But they do exist; we have all seen them" (p. 188). Dawkins is right: we *have* all seen spider webs and, as a result, they have attracted extensive study. Improbable traits have even turned into models: spider web material properties inspire engineered designs (Swanson et al. 2006), and many aspects of their design have been studied (Eberhard 1990). Perhaps spiders' webs are too famous to be considered 'improbable'. Consider an improbable behavior: shrimp parades. In Thailand, thousands of freshwater shrimp crawl onto land at night in September to parade upstream. Having observed this strange behavior, Hongjamrassilp et al. (2021) tested a series of hypotheses and uncovered a likely function (it is a way to migrate upstream while avoiding rapids). This is the inverse-Krogh approach.

Many other complex organismal traits might be improbable, such as keratin-based feathers in birds (Prum 2005) or asynchronous muscle in insects (Josephson et al. 2000). If life independently evolved on another planet, we might imagine that similar ecological processes would cause convergent evolution of organisms that fill some of the same niches as we have here on earth, especially the broadest niches, such as predators and prey (Losos 2017). But would the same improbable traits evolve, including "key innovations" (Blount et al. 2008; Lynch 2009) that characterize single clades, such as spider's webs, or feathers (Prum and Brush 2002), or asynchronous muscle (Josephson et al. 2000)? Who knows if re-running a billion years of evolution would again produce spider webs or feathers or shrimp parades (Blount et al. 2018). Under strict application of the Krogh principle, such improbable traits will tend to remain undiscovered and unstudied.

Importantly, the existence of some "improbable" traits was predicted by theory. In comparative biomechanics and functional morphology, one puzzle or paradox concerned why some animals were such proficient jumpers. For example, bushbabies (*Galago*) (Aerts 1998) and frogs (Astley and Roberts 2012; Peplowski and Marsh 1997) seemed to be able to produce more mechanical power for jumping than should be possible for vertebrate muscle. Theoretical research by Alexander (1974) and others had predicted the existence of "power amplification," as it later came to be called, or elastic energy storage, in the tendons in series with limb muscles, but it took almost four decades to compile sufficient experimental confirmations of these predictions (e.g. Astley and Roberts 2012; Lutz and Rome 1994). Consequently, old ideas that tendons functioned like rigid cables and muscles did all of the mechanical work in motion were overturned; a major paradigm shift in the field. Alexander's (1974) original work and follow-up studies did not present explicit hypothesis; they were implicitly asking a curiosity-driven question "Can we use what we know about anatomy and mechanics to understand how a dog jumps?" Analogously, arguably one of the greatest ideas in physiology is the sliding filament hypothesis for muscle contraction, which proposed that myosin filaments slide (using cross-bridge attachments) relative to actin filaments within a sarcomere to generate force- and velocity-dependent properties based on overall sarcomere length, thereby generating motion. This hypothesis was developed by Huxley and Niedergerke (1954) and Huxley and Hanson (1954), and was theoretical in origin and not empirically demonstrated until ~1985 (Yanagida et al. 1985). Similarly, the search for the structure of DNA was theory-driven, in which several (wrong) theories for the structure of DNA were proposed and then eventually discarded when appropriate empirical data were collected.

Other considerations in choosing organisms and/or questions

Extremes

Many considerations can go into picking a study species. Indeed, Dietrich et al. (2020) present a framework with 20 criteria for choice of a study species (their table 1). One criterion they discuss under the headings 'Responsiveness' and 'Comparative Potential' is the long-standing tradition in comparative, ecological, and evolutionary physiology of focusing on organisms that live in extreme environments, have extreme life histories, and/or possess extreme traits (Adriaens and Herrel 2009; Green et al. 2018). The phrase "outliers" has also been used in this context (Singer 2011).

With respect to extreme environments, we are naturally curious about how anything can live in a place inhospitable to our own kind, such as a hot, dry desert, or the Arctic or Antarctic. From a more coldly scientific perspective, such organisms seem likely to have evolved adaptations that allow them to function, survive, and reproduce in those environments (Garland and Carter 1994; Green et al. 2018). To quote Bartholomew (1987), p 16: "The study of physiological adaptations to extreme environments - the polar regions, the tops of high mountains, ... - has the attraction of allowing an investigator to focus on those aspects of an organism's physiology that allow it to cope with overt, clearly definable challenges such as extremes of temperature, ..., low partial pressures of oxygen, ..." Accordingly, some of the earliest attempts to study ecologically relevant physiology focused on organisms from extreme environments (Cowles 1939; Schmidt-Nielsen et al. 1956; Scholander 1955; Scholander et al. 1953). As an added benefit (or curse), "Such organisms often force one to abandon standard methods and standard points of view" (Bartholomew 1982 p. 234).

Although the end result of natural selection in extreme environments may often be extreme traits, such as the large kidneys of many desert rodents (Al-kahtani et al. 2004), not all organisms from extreme environments will have evolved specialized aspects of morphology or physiology. In particular, some may simply avoid extreme conditions via behavior (e.g. Bartholomew 1964). For instance, most rodents living in hot deserts tend to spend the day underground in burrows, in a cooler microclimate that avoids heat and desiccation.

Aside from adaptive evolution in response to natural selection, sexual selection often leads to the evolution of extreme traits, including extreme morphology like elongated eye-stalks of stalk-eyed flies (Baker and Wilkinson 2001), extreme muscles used in displays (Fuxjager et al. 2016), or extreme behaviors, such as hummingbird courtship dives (Clark 2009). These, too, have sometimes become models, as in studies of muscle trade-offs (Tobiansky et al. 2020) and CJC's studies of sound production during hummingbird courtship dives (see above).

Phylogenetic relationships

Another consideration in picking a study organism is their phylogenetic position. Do they have relatives that may be easily available, or not, or that may live in more or less extreme environments? This is a massive topic and we do not have the space here to do it justice, but we can echo a few points that have been made in the literature (Garland 2001; Garland and Adolph 1994; Garland et al. 2005; Huey et al. 2019; Rezende and Diniz-Filho 2012). Many comparative physiologists are interested in how a trait evolved, which entails comparing multiple species within a clade with the use of statistical procedures that incorporate independent information on phylogenetic relationships. Cherry-picking for study only the most extreme species within a clade can lead to overestimation of the commonness of adaptation; thus, it is important to include mundane (not extreme) species in phylogenetic analyses as well. Therefore, in deciding which species to study, where it falls within the clade of interest is relevant. For example, it may be important to include species from the end of a long branch at the base of a clade or that are sister to a species of particular interest (e.g. see Garland and Ives 2000).

In principle, including extreme species in an interspecific comparative study should increase the statistical power to detect relationships between phenotype and environment, and hence to discover evolutionary adaptations (Garland and Adolph 1994), or to test for coadaptation of different traits. Once discovered, some of these adaptations have been highlighted because they can provide an experimentally convenient avenue to study physiological mechanisms (Green et al. 2018). For example, the guts of snakes have coadapted with their feeding ecology (Secor 2005). Specifically, species that feed infrequently often have the ability to down-regulate the size and functional capacities of the gut, then regrow it rapidly after they eat.

However, choosing extreme species may also have led to a bias in our data base and hence in our view regarding the commonness of evolutionary adaptation to the environment (Garland and Adolph 1991; see also Green et al. 2018). In similar fashion, trade-offs may occur most commonly in organisms that have extreme phenotypes or live in extreme environments (Garland et al. 2021), so a focus on such organisms may bias our view of how common trade-offs really are. More generally, extreme organisms may be unique, such that principles learned from them may lack generalizability; if so, then they are actually unsuitable as general models (Green et al. 2018). A related issue is the peril of assuming that an organism living in an extreme environment necessarily has extreme adaptations. For example, Bartholomew and colleagues initially interpreted the physiology of the marine iguana to be an adaptation to its extreme (i.e., marine) lifestyle, but then had to reappraise this interpretation after studying the physiology of related lizards (Dawson et al. 1977).

Multiple meanings of "model"

A possible source of confusion exists. The Krogh principle holds up convenient organisms as "models" for problems, questions or phenomena. But what is a model organism? The word model has multiple meanings, two of which we highlight in Table 1 (Leonelli and Ankeny 2013; Russell et al. 2017). Biology uses other types of models as well, including physical models (e.g. Emerson and Koehl 1990), mathematical models based on optimality assumptions (e.g. Taylor and Thomas 2014) or numerical/computational simulations (e.g. Bishop et al. 2021; Garland et al. 2021), and verbal or graphical models (Romero et al. 2009), but they are beyond the scope of this paper.

In the sense of the Krogh principle, models relate to questions: a model is any organism in which "design" principles can be studied relatively easily (Table 1). Understanding gained from such models can then be applied inductively to organisms in which form or function cannot be studied as easily. This inductive application to other organisms is the representational scope of the model (sensu Ankeny and Leonelli 2011): the wider set of phenomena that study of the model organism is intended to elucidate. If a frog is a model for jumping, then the representational scope is all animals capable of jumping (Table 1). Under this definition, an unusual, rare or poorly-studied species may nonetheless be a model: snailfish may be a model for how life deals with extreme pressure (Gerringer 2019). Such "Krogh models" may have narrow representational scope or similarity to other organisms, but are chosen for characteristic features that make a given trait or mechanism experimentally accessible (Green et al. 2018).

The other definition of model (Table 1) applies to specific organisms about which science has made substantial advances in unraveling how they work, such as species in the genera *Escherichia, Arabidopsis* ("the plant"), *Caenorhabditis* ("the worm"), *Danio* ("the fish"), *Gallus* ("the bird"), and *Mus* (Ankeny and Leonelli 2011; Bolker 2012). This type of model is already so well-known that they become the default subjects of study for many questions in part because they are already well-known (Dietrich et al. 2020). Being well-known makes them convenient in various ways, including logistically. For example, laboratory strains of mice (*Mus*) have been studied so much that there is a large commercial market for devices designed to facilitate data collection on them, such as devices to allow high-throughput measurements of blood pressure from cuffs placed on the tail, electrocardiograms from unrestrained individuals, and stride characteristics as they run on a treadmill (Claghorn et al. 2017; Kay et al. 2019; Kolb et al. 2013).

The term "model organism" has become so commonly used that researchers often highlight their use of "non-model organisms" (Galván et al. 2022; Russell et al. 2017). Non-model organism research has the disadvantage that it cannot build on the vast foundations of knowledge regarding model organisms and the techniques that work best on them (Dietrich et al. 2020). Studying non-models can seem inefficient, requiring acquisition of new basic knowledge (and new equipment, etc.) before deeper questions may be asked of them. On the other hand, acquiring that new basic knowledge is inherently valuable and also might lead to surprising insights along the way. For example, new "model organisms in the making" might be uncovered (Galván et al. 2022; Russell et al. 2017), such as rattlesnakes for their tail shaker muscles (e.g. Moon and Tullis 2006) or naked mole rats for their thermoregulatory physiology, as noted in the next section.

Model organisms "evolve" and can be created

Naked mole rats (*Heterocephalus glaber*) are, as the name indicates, nearly hairless rodents that are blind and live in underground burrows in amazing eusocial colonies. Indeed, they are one of only two truly eusocial mammals, whose colonies include a single breeding female and a "soldier" caste. Although this breeding system was what attracted the initial research interest on these unusual animals, along the way, biologists soon noticed many other unusual characteristics, including low metabolic rates, poor thermoregulatory abilities, long life spans, and resistance to cancer. Thus, naked mole rats became models for the study of other phenomena, including the basic cellular and molecular processes of both aging and cancer (Green et al. 2018; Keane et al. 2014; Shi et al. 2010; Welsh and Traum 2016).

Giraffe provide a somewhat similar example. These animals, simultaneously wondrous and ungainly, interested early evolutionary biologists, Charles Darwin among them. Despite a century and a half of study, we still don't understand precisely why giraffes have their most salient feature: such a long neck. Browsing benefits and/or sexual selection are the prevailing hypotheses (Mitchell et al. 2009; Switek 2017). Much later, physiologists began studying their blood pressures (which are high), wishing to understand their cardiovascular function and how they could regulate pressure and blood flow to the brain as the head moved (rapidly) from far below to far above the position of the heart (references in Powers et al. 2012; White and Seymour 2014). In this regard, they served as models for understanding how long-necked sauropod dinosaurs might have coped. The giraffe-to-sauropod inference has led to the speculation that the longest cells in the history of life were the recurrent laryngeal nerves in sauropods (Wedel 2012).

In considering the Krogh principle, Bennett (2003, p. 1) posed the question: "what if an organism with the desired properties does not exist?" He argued that an extension of the Krogh principle would be to create novel organisms ideally suited for the study of particular physiological phenomena. Among various ways that this might be done (e.g. transgenesis), he emphasized selection experiments and experimental evolution, which allow the study of cross-generational changes in real time (Garland and Rose 2009). Bennett offered three examples, the first involving artificial selection for voluntary locomotor activity in laboratory house mice and the other two using laboratory natural selection (experimental evolution *sensu stricto*) to favor desiccation tolerance in fruit flies (*Drosophila melanogaster*) and adaptation to high temperature in bacteria (*Escherichia coli*). The first of these examples was conducted by one of us (TG), a recovering herpetologist, so we will provide some rationale and highlights.

The original grant to conduct the "High Runner" mouse selection experiment, which TG describes in the following paragraphs, was provided by the National Science Foundation in 1991. The stated purpose was "to elucidate the genetic and physiological mechanisms underlying individual differences in voluntary wheel-running behavior," which would "allow direct test of the long-standing hypothesis that behavior tends to evolve more rapidly and prior to changes in underlying physiological capacities." Further, the proposed research was "a logical extension of" TG's previous studies with lizards and snakes "because it will allow analysis of the genetic basis of individual variation in locomotor behavior in much greater detail than is possible with reptilian systems." Thus, TG turned to lab mice because they were a "convenient" (Krogh 1929) and practical "model" for studies of the genetics and physiology of locomotor behavior. As compared with lizards and snakes, mice have short generation times and have been studied intensively, thus offering a wealth of background knowledge within which to interpret new results. Moreover, many tools for the study of mice have been developed over the decades, including standardized behavioral tests and genetic/genomic methods. Finally, mice are also mammals, which increased the probability that findings might have applications for veterinary or human health, as well as possible funding from the U.S. National Institutes of Health.

The High Runner selection experiment includes four replicate lines bred for high wheel running on days 5 and 6 of a 6-day period of wheel access as young adults (HR lines), as well as four non-selected Control (C) lines that are bred without regard to their running (Swallow et al. 1998). Many of the key findings from the High Runner mouse experiment can be found in review papers (Garland 2003; Garland and Rose 2009; Rhodes et al. 2005; Wallace and Garland 2016). Briefly, all four HR lines evolved rapidly and reached apparent selection limits after 17-27 generations, at which point they ran, on average, about 3-fold more than mice from the C lines. However, a trade-off evolved between the average speed and duration of daily wheel running among the four lines, one of several examples that mean the HR mice can serve as models for biological trade-offs (e.g., see also Belke and Garland 2007). When housed without wheels, HR mice are more active than C in their home cages.

At lower levels of biological organization, the HR lines have evolved in both their brains and bodies, i.e., changes in both motivation and ability for voluntary wheel running. For example, they have evolved larger brains and they are more sensitive to Ritalin, the latter leading to their proposed use as a model for human Attention Deficit Hyperactivity Disorder (ADHD). As another example, the HR lines have evolved smaller muscles and other muscle changes that may underlie the evolved speed-duration trade-off in voluntary exercise behavior. Sex differences have emerged for various traits, meaning that the HR lines may serve as models for the evolution of sexual dimorphisms. In these examples, the creation of new "models" was a serendipitous byproduct of the original experimental goals.

Pitfalls of the inverse-Krogh principle

The inverse-Krogh approach to research does have a couple major pitfalls. If you pick your organism first, then you *must* ensure the questions you ask are both interesting and tractable. To paraphrase a reviewer, picking an organism just because it is poorly studied, then vaguely wishing to discover something interesting about it, is not sufficiently focused. Upon considering an organism, it is essential to frame research by finding a suitable (tractable) research question. This will be easier for some organisms than for others. Here are some obvious examples where question and organism are not tractable. Captive studies are not feasible on organisms that cannot be housed in captivity, and for those that can, complicated or expensive husbandry needs may limit what can be done. Organisms that are large or have long lifespan can be a challenge to study, even though they are ecologically and evolutionarily relevant, so studying them may be especially conceptually valuable. It would be very hard to get a live elephant into your physiology laboratory on most university campuses, let alone a sample size of 10 or more of them. Organisms with lifespans longer than a few years will be difficult subjects for a captive breeding experiment. One can waste a lot of time and money searching but failing to find a species that is rare. For threatened or endangered species, the pitfalls may be legal or ethical: such species have many aspects of their biology that cannot be studied, no matter how easy they are to catch and handle, because research permits for invasive procedures cannot be obtained. Large charismatic species also have similar limits. Species that live in geopolitically inaccessible locations such as active war zones cannot be reached. Research that requires a lot of money is impractical if you do not have a grant. These caveats could also apply to the Krogh principle. We mention these obvious examples to set the stage for less-obvious ones.

Mismatches between organism and question can be subtle. In some instances, the biology of the organism "feels like" it should be or at least could be well-suited for research on a particular topic, but unfortunately, just isn't. For instance, male hummingbirds perform flamboyant, obvious courtship displays to females, and these displays are highly tractable for certain analyses (Clark and Mistick 2018; Hogan and Stoddard 2018). But measuring female preferences for displays; that is, studying the nature of the sexual selection that has driven the evolution of these male phenotypes has proven hard to assess in hummingbirds. Female choice has been studied in wild birds species, such as sage grouse, where copulation takes place in the open on a male's territory (Patricelli et al. 2002), or in manakins, which are large enough that females can be instrumented with radio telemetry to track their movements (DuVal and Kapoor 2015). As such, these species are "Krogh models," permitting study of female choice in the wild. Hummingbirds are too small to carry such devices, and they fly fast, which makes them harder to follow than other birds. Although female preferences of hummingbirds may or may not be impossible to study, it appears it will always be harder to study than in other birds.

When engaged in the inverse-Krogh approach, the researcher must continually assess: is this research going to yield results interesting to the broader scientific community often enough to be worth the effort? Of course, this question might be impossible to answer with certainty in real time. If, mid-study, you are slowly coming to the realization that your chosen species is yielding rather mundane results, consider placing your results in a phylogenetic perspective: does your mundane species have interesting relatives? For example, CJC has collected data on courtship displays of nearly 30 species of "bee" hummingbirds. Certain of these species were unique in one way or another, such that it was natural to write a paper focused on that species (e.g. Clark et al. 2013b). But other species are less-unique when considered individually, hence less likely to be studied and harder to find an angle when writing a paper focused on them. But these "mundane" species still play a critical role in characterizing interesting phylogenetic patterns. For instance, while many hummingbirds have socially learned song, like in songbirds or parrots, a few don't. Negative results can be challenging to present at the level of an individual species; a paper titled "White-bellied Woodstar (*Chaetocercus mulsant*) does not sing" might have trouble being published. But this same result, in phylogenetic context (Clark et al. 2018), showing that it is a derived loss of this complex trait, has been of interest to neuroscientists.

A related problem can be finding your species is hard to study, such that you have few results relative to the effort you have put in. Dr. Patricia Brennan found this to be true for her Ph.D., in which she decided to study Tinamous, a Paleognathae bird clade that is closely related to ostriches and other large flightless birds. These birds interested her because they are easy to hear at dawn and dusk in Colombia, where she grew up, but scientifically they were poorly known. Having picked her organism first, she studied their mating system and tendency to lay non-camouflaged eggs in nests on the ground (Brennan 2010). Tinamous are notoriously secretive, shy of people, and mainly found in thick neotropical jungles, characteristics that together make them an especially difficult group to study (Brennan 2004). In short, under the Krogh principle, tinamous are not a likely species to pick for a research question in ecology: they are incredibly inconvenient (Bishop et al. 2021 notwithstanding)! Late in her Ph.D. research, Dr. Brennan was lucky enough to actually witness copulation, and noticed something bizarre: an enormous, weirdly twisted "worm" dangled from the male's cloaca for the next few minutes until it slowly crawled back inside him! Had copulation partially dislodged some sort of enormous internal parasite? As ornithology courses used to teach that birds do not have an intromittent organ (only a few do have one), she at first did not realize that this corkscrew-shaped structure was the male tinamou's penis. Although studying the reproductive functional morphology of tinamous was not convenient, another early-diverging bird clade, ducks (Anatidae), also have corkscrew-shaped penises similar to tinamous. As many duck species are kept in captivity, they were more convenient to study. Thus, an initial observation on tinamous sparked a research program on the rootward bird clades that do have a penis, such as duck and ostriches (Brennan et al. 2017; Brennan and Prum 2012). This was then followed by work on vertebrate genitalia functional morphology and coevolution on taxa spanning dogfish to dolphins (Brennan et al. 2021; Hedrick et al. 2019). Dr. Brennan's research program started as inverse-Krogh (research on tinamous) before shifting to Krogh (research on duck penises).

Another potential problem is picking the organism first, the research question second, but then presenting the research as if one arrived at the organism and question by following the Krogh approach. This sort of after-the-fact justification in science (see also Rowbottom and Alexander, 2012) can even lead to HARKing: Hypothesizing After the Results are Known (Kerr 1998). As a hypothetical example, if one discovers a turtle that actually can jump, this does not mean that turtles are now a good "model" for understanding jumping. Supposing this turtle has adaptations for jumping, it may be of interest to study convergent evolution, or trade-offs (Garland et al. 2021), or multifunctionality, or another similar question. In contrast, one might argue from a Krogh-principle based perspective that studying the inability of turtles to jump well may give insight regarding general constraints on jumping ability. In any case, the danger of HARKing can be avoided by preregistration (Nosek et al. 2018).

A final pitfall, noted by all three reviewers, is practical: funding for research explicitly motivated by the inverse-Krogh principle is often difficult to attract. Accordingly, Dietrich et al. (2020, their table 1) listed "Financial Considerations" as one of 20 criteria for organismal choice. Generally, grant proposals are framed around research questions, rather than focal species. (Exceptions may occur, as when funding is available for the conservation biology of a particular species.) Aside from small projects that fall at the "one-and-done" end of the spectrum, beginning any research program demands due consideration of the potential for funding. Many interesting organisms that might be approached from an inverse-Krogh perspective live in areas that are not easy to access or are otherwise difficult to study without somewhat expensive technology. Fortunately, many organism-oriented societies (e.g., for reptiles, birds or mammals) offer small grants, often slanted towards graduate students. State agencies may offer conservation-oriented grants appropriate for interesting organisms. Moreover, as noted above in the section on "Model systems can be created," some unusual/extreme/interesting organisms have been developed into models. In any case, we acknowledge that some questions or organisms probably should not be approached until *after* one obtains tenure or its equivalent, as was the case with TG's mouse selection experiment.

Final thoughts

We wrote this piece to emphasize that research does not always need to be shoehorned into "organism X is a model for question Y" to have merit. (Perhaps, too, we feel guilty for having participated in graduate oral exams where students were pushed to make just such an argument!) Careful consideration of some of our examples will reveal that the arguments we have advanced are not specific to the "inverse-Krogh" approach. For instance, the pitfalls noted in the previous section can also apply to the Krogh approach. Research breakthroughs are rarely simple enough to fit neatly into just one category; more often, they have both "Krogh" and "inverse-Krogh" elements. The line between the Krogh and inverse-Krogh principles can be a fine one; research programs often incorporate both (Figure 3). Also, Ray Huey pointed out in review comments that we have largely overlooked a corollary to the Krogh approach, which runs concept-to-model. In his words, "if there's a conceptual or theoretical idea that is worth exploring, pick an animal that is suitable for study." TG's High Runner mouse selection experiment (see above) would fit this bill, as it was designed to study the correlated evolution of behavior and physiology in a general sense and, more specifically, the behavior evolves first hypothesis. It also serves as an example of Bennett's (2003) point about creating convenient models if nature has not provided them.

Science is built on curiosity, creativity, exploration, and innovation -- combined with high motivation. Most discoveries lead to new questions, in part because we just don't know what we don't know. As an organized human enterprise, science is only about 200 years old (Bartholomew 1982). What will science look like hundreds or even thousands of years from now? It is impossible to say. Suppose that in 10,000 years, the sum total knowledge about all organisms is assessed. No doubt some organisms – models – will have more known about them than others. Surely we will know less about snailfish (*Pseudoliparis*) from the Mariana Trench than about *Mus* or *Drosophila* or *Arabadopsis*. The inverse-Krogh principle does not predict that we will ever know as much about snailfish as we do *Drosophila*. However, research guided by the inverse-Krogh principle will lead us to learn *something* about many more organisms. The organisms we will learn the most about are those most accessible for study: some combination of straightforward to find or observe, easy to catch, easy to hold (and maybe to breed) in captivity, and research permits can be obtained. With respect to research questions, the literature, particularly old or obscure work, often contains interesting observations that can be useful prompts for new research questions about a poorly-known species.

Predicting what the future holds (for scientific research) is always difficult. Scientific discoveries are by their very nature unpredictable. To quote Yogi Berra, "You've got to be very careful if you don't know where you are going, because you might not get there." Indeed, "discovery" refers to learning or finding something for the first time. Which organisms will provide the greatest number of insights about the nature of biological life is impossible to know in advance. Thus, students in search of research topics might do well to follow the Krogh Principle. But they should not forget the inverse-Krogh principle, in part because a love of particular organisms may go a long way towards maintaining their motivation for doing science in the face of inevitable hurdles and setbacks. If you love snakes, then study snakes (Greene 2000; Lillywhite 2021)!

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Author contributions

JH wrote a tweet about the inverse-Krogh principle in 2012. CJC cited JH's tweet in a guest lecture for TG's undergraduate class in ecological and evolutionary physiology; TG suggested turning the lecture into a paper. All authors contributed to writing.

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Table 1: Definitions

Name	Definition	Example	Reference
Model (standard)	"a non-human species that is extensively studied to understand particular biological phenomena" - Wikipedia (accessed Jan 12, 2022) "non-human species that are extensively studied in order to understand a range of biological phenomena, with the hope that data, models and theories generated will be applicable to other organisms, particularly those that are in some way more complex than the original" (Leonelli and Ankeny 2013, p 209)	*E. coli,* "the plant" *Arabidopsis thaliana ,* "the worm" *Caenorhabditis elegans,* "the fish" *Danio rerio,* "the bird" *Gallus gallus,* "the mouse" *(Mus musculus)* "the rat" *(Rattus rattus)* "the frog" *(Xenopus laevis)*	(Ankeny and Leonelli 2021; Bolker 2012; Leonelli and Ankeny 2013)
Model (Krogh)	"For a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied." (Krogh 1929, p. 247) any organism in which certain "design" principles are most conveniently studied "Krogh organisms" (Green (Green et al. 2018)	"... my teacher, Christian Bohr, was interested in the respiratory mechanism of the lung and devised the method of studying the exchange through each lung separately, he found that a certain kind of tortoise possessed a trachea dividing into the main bronchi high up in the neck, and we used to say as a laboratory joke that this animal had been created expressly for the purposes of respiration physiology." ~~~~ Frogs as models of jumping	(e.g. Bennett 2003; Green et al. 2018; Krebs 1975)
Negative model	Organism that does not exhibit a human disease or disorder	Mammals that hibernate and put on extreme amounts of body fat	(Green et al. 2018)

		without adverse health consequences	
Representational target	"the phenomena to be explored through the use of the experimental organism"	Jumping, in "frogs as models of jumping"	(Ankeny and Leonelli 2011, pg 315)
Representational scope	"how extensively the results of research with a particular experimental organism ... can be projected onto a wider group of organisms."	Other organisms that jump, in "frogs as models of jumping"	(Ankeny and Leonelli 2011, pg 315)

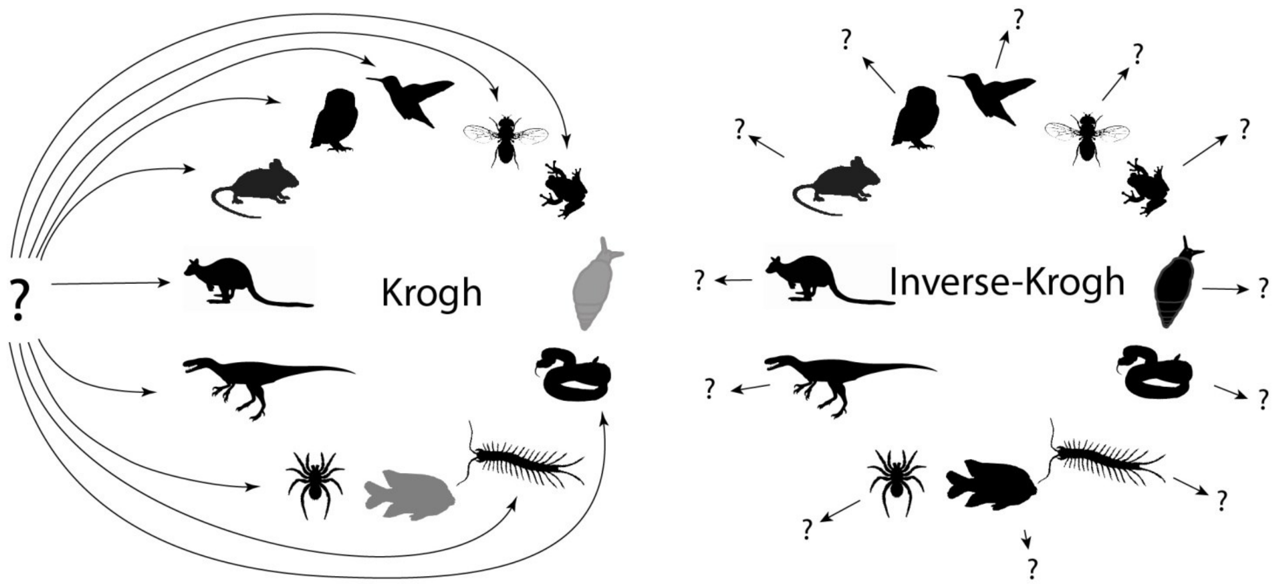

Figure 1. Under the Krogh principle (left), research begins with a question and then finds a suitable organism, most commonly one that breeds well in captivity, has been adapted to laboratory conditions, is convenient or cost-effective to study, or has been the subject of much previous research (e.g., *Arabidopsis*, *Drosophila*, *Mus*). This approach potentially leaves some organisms, in gray, under-studied. In the "inverse-Krogh" approach espoused here (right), research begins with an organism then seeks suitable research question(s). Silhouettes are from phylopic.org.

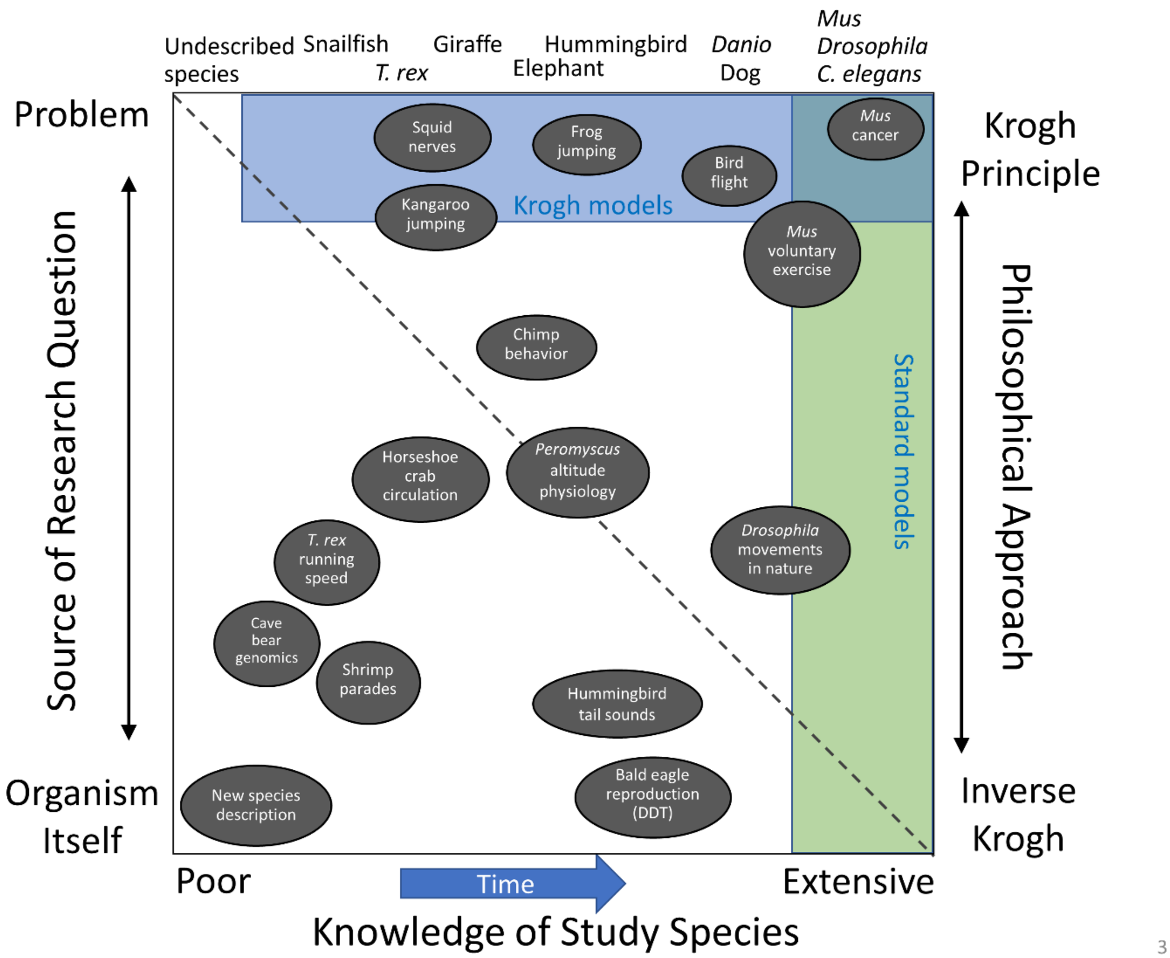

Figure 2. Research questions arise out of some combination of observation of the organism itself (inverse-Krogh), or out of a pre-existing, pre-defined 'problem' to be studied (Krogh). Any given species has a certain amount of pre-existing knowledge about it; under the "standard model" definition (Table 1), models are the species for which the most extensive knowledge exists. By contrast, under the "Krogh model" definition (see text), a model species may be poorly known (generally) but useful for understanding a particular problem. Over time, knowledge about any given species tends to progress towards the right.

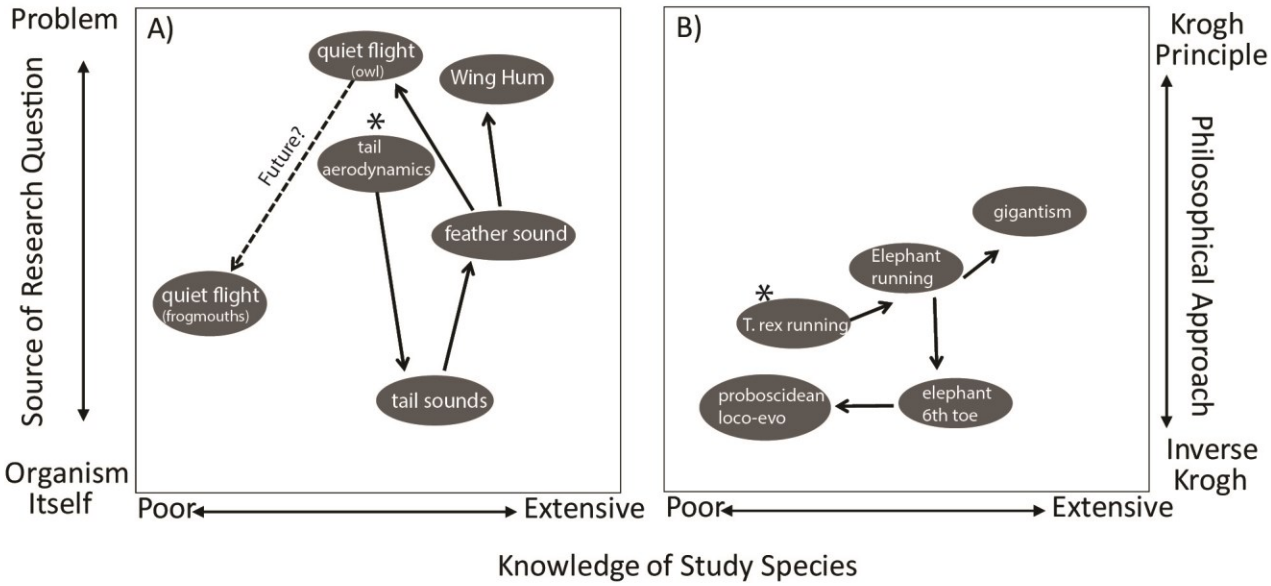

Figure 3. This figure uses the framework of Figure 2 to illustrate the paths of two research programs that have shifted naturally shift between Krogh and inverse-Krogh questions. A) CJC's work on how bird flight makes sound. B) JRH's work on locomotion of giant land vertebrates. * start