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HOW FAST DO MOBILE ORGANISMS RESPOND TO STIMULI?

RESPONSE TIMES FROM BACTERIA TO ELEPHANTS AND WHALES

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SUMMARY

Quick responses to fast changes in the environment are crucial in animal behaviour and survival, for example to seize prey, escape predators, or negotiate obstacles. Here, we study the 'simple response time' that is the time elapsed between receptor stimulation and motor activation as typically shown in escape responses, for mobile organisms of various taxa ranging from bacteria to large vertebrates. We show that 95 % of these simple response times lie within one order of magnitude of the overall geometric mean of about 25 ms, which is similar to that of a well-studied sensory time scale, the inverse of the critical flicker fusion frequency in vision, also lying within close bounds for all the organisms studied. We find that this time scale is a few times smaller than the minimum time to move by one body length, which is known to lie also within a relatively narrow range for all moving organisms. The remarkably small 10^2-fold range of the simple response time among so disparate life forms varying over 10^{20}-fold in body mass suggests that it is determined by basic physicochemical constraints, independently on the structure and scale of the organism. We thus propose first-principle estimates of the simple response and sensory time scales in terms of physical constants and a few basic biological properties common to mobile organisms and constraining their responses.

1. INTRODUCTION

The concept of timescale is fundamental in science. An important timescale in biology is the minimum response time of mobile organisms to a dynamic environment. When an animal suddenly encounters a prominent event such as a prey, a predator or an obstacle, it must react fast enough, albeit not faster than necessary, in order not to sacrifice accuracy or waste the energy or space dedicated to its sensory systems (e.g. Attwell and Laughlin 2001). For a response to be fast enough, the information that produced the response should not be outdated (e.g. Spence 2009), which requires in particular that the response time does not exceed the movement duration and that the animal position has not changed much. For animals moving with legs, the response time is often compared to the stance or step duration (e.g. More et al. 2018); however, for animals not equipped with legs, a more general time scale for comparison with the minimum response time is the minimum time to move by one body length, that is the ratio of body length to maximum speed.

The maximum speed of terrestrial and aquatic organisms has been found to be roughly proportional to their body length, from bacteria to large vertebrates (Bonner 1965, McMahon and Bonner 1983), contrary to the preferred speed which is subjected to different constraints (e.g. Bejan and Marden 2006). These results, later confirmed with a large data set, imply that the time to move by one body length at maximum speed lies in a narrow range around one tenth of second within a factor of ten, for running and swimming organisms of mass varying by 10^{20}-fold in body mass. The ubiquity of this minimum locomotion time scale, holding for so different organisms' structures and sizes, whereas characteristic biological timescales cover more than 12 orders of magnitude (e. g. Shamir et al. 2016), suggests that it is bounded by universal constraints, and led Meyer-Vernet and Rospars (2015, 2016) to propose a tentative interpretation

based on the mass density of living organisms, the maximum specific tension exerted by molecular motors and muscles (Rospars and Meyer-Vernet 2016) and the maximum mass specific metabolic rate (Weibel and Hoppeler 2005, Glazier 2014, Makarieva et al. 2005), which constrain the maximum speed and remain within close bounds for all moving organisms.

The question therefore arises of whether a similar result could hold for the minimum time to react to stimuli. The scaling of sensorimotor delays with body mass in relation to movement duration has been studied by More and Donelan (2018) for the stretch reflex in terrestrial mammals, but there is no large-scale study of the minimum response time covering the entire mass range of mobile species. We therefore collated data from the literature for the 'simple response time', that is the time to detect the occurrence of a simple stimulus, as determined from behavioural and electrophysiological measurements in various taxa from free-living cells to large metazoans like sharks, turtles, and elephants, spanning 20 orders of magnitude in mass from 10^{-16} to 3900 kg.

An important constraint to fast response is set by sensory limitations that affect the ability to track fast moving objects such as prey or mates. These limitations have been studied in the case of vision, using the critical flicker fusion frequency (CFF), defined as the frequency at which a flickering light is indistinguishable from a continuous light (e.g. D'Eath 1998). The scaling of this property with body mass and metabolism has been studied by Healy et al. (2013) for vertebrates; we collated the corresponding characteristic time (1/CFF) and extended the data to compare it to the minimum response time.

Our aims are (i) to determine whether the minimum response time remains within close bounds across the whole of mobile life despite the diversity of structures and mechanisms, (ii) to compare it with the minimum sensory time-scale for vision (inverse of the critical flicker fusion frequency) and to the minimum time to move by one body length, and (iii) to propose an

interpretation based on basic physicochemical and biological properties. Because the response times of animals are expected to be hugely different from those of microorganisms, which are subjected to very different constraints (e.g. Martens et al. 2015), we also investigate the timescales separately for single cells and for metazoans.

The empirical data are studied and discussed in sections 2 to 4. Section 5 proposes order-of-magnitude interpretations based on fundamental physicochemical constants and basic properties of life, with conclusions given in Section 6.

2. MATERIAL AND METHODS

2.1. *Data Collection*

We define as "simple response time" (T_S) the time to detect the occurrence of a simple and sudden stimulus. These T_S are delays from the time at which the stimulus reaches the organism to either the onset of movement – measured by behavioural methods (for example with high-speed cinematography), or to muscle activation – measured by electrophysiological methods with direct recordings from muscles (electromyogram EMG). Since our study concerns minimum response times, it does not include the "discrimination (or identification) and choice response times" (e.g. Luce 1991). In these complex tasks, the subject, whether animal or human, is presented with one of several stimuli and has to respond to only one of them (discrimination, e.g. Blough 1978) or to perform different responses depending on the stimulus presented (choice between stimuli, e.g. Abraham et al. 2004). Likewise, for microorganisms, we only considered the response delay after a stimulus (e.g. Block et al. 1982), which only involves internal time scales of the organisms and is shorter than the time based on the comparison of different measurements, which depends on

ambient conditions (e.g. Mitchell 1991). Thus, our definition of simple response times T_S being based on the simplicity of the task and the stimulus does not take into account the length, variability or underlying sensorimotor mechanisms of the response delays (Roeder 1963, Koch 1999, Herberholz and Marquart 2012, Sillar et al. 2016, Roberts et al. 2019). It avoids the operational difficulty to implement these multiple criteria and insures a better representativeness of the sample.

We searched the Google Scholar database and extracted simple response times and other relevant data (species names, stimuli, experimental conditions, etc.) published in refereed journals. Our main objective being to investigate the interspecific variability, we kept all values found for non-human species, but not for humans, for which we considered only a selection of papers, either classical or illustrating the diversity of experimental paradigms. For a given species and stimulus, we tabulated simple response times as the mean provided by the authors, or the mean of the extremes when given as a range.

Our T_S sample (Table S1) includes 175 measurements on 81 species. Behavioural (n = 134) and electromyographic (EMG, n = 41) measurements (column M in Table S1) are not significantly different (Fig. S2A and Table S10); thus, we pooled them together in subsequent analyses. The data belong to two main classes: startle and non-startle. “A startle response is an abrupt response, often of relatively short latency, to a sudden stimulus that we believe to be both unexpected and alarming (i.e., of high valence)” (Bullock 1984), so that threats that develop gradually are excluded. Startle responses form a homogeneous class gathering the majority of measurements (73 %) and of species (68 %, multicellular only). They may result in a large movement translating the whole body (escape, called fast-start in fishes, 86 measurements on 50 species) or in small movements (called sometimes ‘eyelid, jaw, etc. reflex’ in birds and mammals, depending on the muscle triggered, 42 measurements in five species). Non-startle

responses (27 % of measurements on 32 % of species) include taxes (in single cells only), reflex control of locomotion, fast limb movements, predatory movements, and a few other fast responses in multicellular organisms. Only six species were tested for more than one response type.

For flicker fusion times T_F, we used the CFF data from Healy et al. (2013) (34 vertebrate species) and Inger et al. (2014) (31 invertebrate species and 41 vertebrate species not considered by Healy et al. 2013), plus 25 other CFF measurements. Our sample (T_F = 1/CFF, Table S2) includes 130 measurements on 108 species. The values measured by behavioural (n = 26) and electroretinographic (ERG, n = 103, column M in Table S2) techniques are not significantly different (Fig. S2C and Table S10); so, we pooled them together.

The minimum times to move by one body length T_L were collected and analysed previously from the measured maximum speeds V_{max} of swimming and running organisms of length L as $T_L = L/V_{max}$; this sample includes 458 measurements from 427 species (Table S3) and does not include flying, whose maximum speed is not constrained by muscles (Meyer-Vernet and Rospars 2016).

For T_S and T_L, we distinguished unicellular and multicellular organisms and spermatozoids (T_L only), as specified in column U of Tables S1 and S3. For the three timescales, column Cla of Tables S1-S3 defines groups of phylogenetically related species; they belong to the same class in multicellular organisms and to the same kingdom according to the WoRMS database (World Register of Marine Species, http://www.marinespecies.org) in unicellular organisms (except spermatozoids). Further details on Tables S1-S3 are given in Supplementary material.

Table S4 lists 14 mammalian species for which both minimum locomotor times T_L and maximum mass specific metabolic rates (MSMR in W/kg) are known.

2.2. *Body Mass*

We characterized body size by the mass M for each species. Except for vertebrates with measured CFFs from Healy et al. (2013) for which we used the mass provided by these authors, we searched the original papers for mass, length or age. When given as a range, we took the mean. We converted length in mass using either the length-mass relationship of the species when it is known or a more generic relationship, for example $M_{kg} = 11.2\ L_m^{3.04}$ which applies to fusiform fishes (Froese et al. 2014; see other relationships in Meyer-Vernet and Rospars 2016). When no indication was provided in the papers, we searched the average mass (or length) of the species in the scientific literature (for example, Bartholomew and Heinrich 1973; Byrne et al. 1988; Niven and Scharlemann 2005, for insects; Falk-Petersen 1981, for shrimps) or in websites. We have not considered in the analyses two T_F data for which the mass could not be found (lines 24 and 87 in Table S2). Otherwise, all body masses and their references are given in Tables S1-S3.

2.3. *Temperature Effects*

In order to check the dependence of the time scales on temperature, we used (in the Discussion section only) the Boltzmann-Arrhenius model from chemical reaction kinetics, which holds approximately for metabolic and locomotor rates (e.g. Dell et al. 2011). This model yields biological time scales inversely proportional to the Boltzmann factor, $\exp(-E/k_B\theta)$, where E is the activation energy of the process studied (in joules), k_B, the Boltzmann constant, and θ, the temperature (in kelvins). Thus, the corrected time scale T_0, at the reference temperature θ_0, of time T measured at temperature θ is $T_0 = T \exp(qE/k_B)$, where $q = 1/\theta_0 - 1/\theta$. For all timescales, we chose $\theta_0 = 20$ °C as reference and $E = 0.66$ eV, the mean activation energy observed in a wide

range of species and traits (Dell et al. 2001). In the special case of T_S, we also applied a finer standardization procedure distinguishing defence or movement away from a stimulus, like startle responses, and consumption or movement toward a stimulus (almost all other responses), whose mean activation energies are E = 0.4 and 0.7 eV, respectively (Dell et al. 2001).

2.4. *Statistical Analyses*

Statistics were computed on either data T or their log-transform ($\log_{10} T$). In the main text, but not in Supplementary material, all data (T and $\log_{10} T$) were averaged per species, counting separately sperm cells (in T_L data, Table S3) and late developmental stages (for *Danio rerio* and *Procambarus clarkii* in T_S data, Table S1). The data in each category (T_S, T_F and T_L) were characterized by their medians and interquartile ranges IQR. Lognormal distributions were fitted after determination of their parameters (mean μ and standard deviation σ) on log-transformed data. However, for easier readability, μ in log units was converted in seconds in text and figures (except in Supplementary material Tables S7-S10), as $\mu^* = 10^{\mu}$ (μ^* is the geometric mean and median of the lognormal distribution fitted to data T). Similarly, σ was expressed as a multiplicative standard deviation $\sigma^* = 10^{\sigma}$ (σ^*, like σ, is dimensionless; it determines the asymmetry of the distribution, and the interval $[\mu^*/\sigma^*, \mu^*\sigma^*]$ covers a probability of 68.3 %, see Limpert et al. 2001). The overall interval of variation in each timescale was expressed as the percentiles 2.5 % and 97.5 %, which are less sensitive to outliers and sampling fluctuations than the minimum and maximum; the ratio of these percentiles and its logarithm (denoted δT_{95}) estimate the multiplicative range including 95 % of values. Statistical distributions were compared with the Kolmogorov-Smirnov test. Least-square regressions of $\log_{10} T_i$ against $\log_{10} M$ and least-rectangle regressions of $\log_{10} T_L$ against $\log_{10} MSMR$ (Dagnelie 2011) were

calculated and given as scaling equations $T_i = T_0 M^{\alpha}$ in figures and their slope (also called scaling exponent) α as 95 % confidence intervals in the text. Tables S7-S10 provide details of ANOVA and multiple comparisons of means using Tukey-Kramer adjustment method. We used the significance level 5 % in all tests. We performed all statistics with the Matlab Statistical Toolbox (The Mathworks, Natick, USA).

3. EMPIRICAL RESULTS

3.1. *Statistical Distributions of Timescales and Comparisons*

Simple response times, T_S, extend from 2.5 ms in the escape behaviour of the calanoid copepod *Undinula vulgaris* to 485 ms in the acoustic response of the white whale *Delphinapterus leucas*, with median 24 ms and IQR 43 ms. The distribution is lognormal (Fig. S1A), with geometric mean $\mu^* = 26$ ms and multiplicative standard deviation $\sigma^* = 3.26$. Critical fusion times T_F range from 2.5 ms in the black fire beetle *Melanophila acuminata* to 250 ms in the crustacean isopod *Booralana tricarinata*, with median 24 ms and IQR 27 ms. The distribution is lognormal (Fig. S1C) with $\mu^* = 25$ ms and $\sigma^* = 2.14$. The times to move by one body length at maximum speed T_L extend from 5 ms for a sea urchin to 2.8 s for a large spirochetes bacterium, with median 71 ms and IQR 99 ms (Meyer-Vernet and Rospars 2016). The distribution is lognormal with $\mu^* = 78$ ms and $\sigma^* = 2.73$ (Fig. S1B). Since most of the variability in the data comes from the diversity of species, stimuli and measurement methods, such lognormal distributions are expected if these factors act in a multiplicative way.

Figure 1 compares as boxplots the (log-transformed) timescales T_F, T_S and T_L. Their relative position is indicated by the medians (central red lines). ANOVA and multiple comparisons of

means show that the sensory timescale T_F and the simple response time T_S are similar, whereas T_L is significantly different and about three times longer (Table S7).

3.2. *Variation with Body Mass*

To study the dependence of simple response times on body mass M for the whole data set encompassing life's major domains, we plotted the pairs (M, T_S) in log-log plots for 81 species (Fig. 2), including microorganisms in the mass range 10^{-16} (bacterium) to 5×10^{-13} kg (green alga) and multicellular organisms from 3×10^{-9} (spider) to 3860 kg (elephant). Fig. 2A distinguishes the taxonomic groups whereas Fig. 2B distinguishes the types of responses. Overall, the mass M varies by a factor of about 10^{20} whereas 95 % of the T_S values lie between 4.7×10^{-3} and 0.31 s (Table 1, first line). Although very small, the slope of the regression line is significantly different from zero (95 % confidence intervals [-0.065, -0.010], Table 2), but as shown in Table 1, this effect results from the larger simple response times in single cells ($\mu^* = 129$ ms) than in multicellular organisms ($\mu^* = 22$ ms). Since this difference is significant (Table S8c, first line, $p < 10^{-3}$), the two groups must be studied separately. The scaling exponents α of the power law regressions in both groups are not significantly different from zero with 95 % confidence intervals [−0.41, 0.49] for single cells and [−0.01, 0.08] for multicellular organisms, whereas the intercepts differ by more than one order of magnitude (Table 2 and Fig 2A).

Flicker fusion times T_F could only be measured in multicellular organisms. Therefore, the body mass of the 106 species shown in Figure 3 only varies from 2×10^{-6} kg (fruit fly) to 354 kg (sea turtle), representing over eight orders of magnitude, whereas 95 % of the T_F values lie between 2.5×10^{-3} s and 0.25 s (Table 1). No effect of body mass on T_F could be evidenced, since the power law regression is $T_F = 0.026M^{\alpha}$ (Fig 3), with α in the 95 % CI [−0.01, 0.06] (Table 2).

The times to move by one body length at maximum speed T_L (Meyer-Vernet and Rospars 2016, Fig. 4) concern 426 species including microorganisms from 10^{-16} kg (bacterium) to 1.3×10^{-8} kg (ciliate eukaryotic cell) and multicellular organisms from 10^{-9} (copepod) to 1.4×10^{5} kg (blue whale). So, M varies by 21 orders of magnitude whereas 95 % of the T_L values lie between 21×10^{-3} and 0.71 s. The times T_L in single cells ($\mu^* = 145$ ms) are twice longer and more variable than in multicellular organisms ($\mu^* = 69$ ms), this difference being significant (Table S8b, second line, $p < 10^{-8}$). In both groups T_L increases slightly with mass, since the 95 % CI of the slope of the regression line α is [0.020, 0.14] for single cells and [0.028, 0.060] for multicellular organisms (Table 2). However, the trend of the multicellular group results from the largest vertebrates since for species under 50 kg the slope of the regression law α is not significantly different from zero (95 % CI is [−0.030, 0.11] (Table 2).

Since the maximum metabolic rate of organisms affects their maximum speed (Meyer-Vernet and Rospars 2016), we studied also the dependence of T_L on maximum specific metabolic rates (MSMR) in 14 species of mammals for which both values were determined (Table S5). The slope of the regression lines of MSMR against body mass (Fig. S6A) and of T_L against MSMR (Fig. S6B) are not significantly different from 0 and −1 respectively, suggesting independence of MSMR on mass and inverse dependence of T_L on MSMR.

4. DISCUSSION

4.1. *Variability and Mass Dependency of Timescales*

Over the whole mass range, the variabilities of the timescales expressed by the ranges including 95 % of the data (δT_{95}, Table 1), are so small compared to the mass ranges (δM, Table 2), that

their ratios are always less than one in a million ($10^{\delta T95}/10^{\delta M}$). Indeed, 95 % of the simple response times T_S (Fig. 2), of the visual resolution times (T_F = 1/CFF, Fig. 3) and of the minimum locomotor times T_L (Fig. 4) lie within less than a factor of ten, five and six respectively of their geometric mean, whereas the mass varies by 20, 8, and 21 orders of magnitude for T_S, T_F and T_L respectively. This is noteworthy, given the diversity of sensorimotor systems and the huge mass range, and suggests that these times are strongly constrained by physics, as was previously proposed for T_L. The small variation of the visual resolution times is remarkable, given the variation in spatiotemporal optical quality with eye size, which is correlated to body size (e.g. Currea et al. 2018), and the large diversity of visual systems (e.g. Fernald 2000) and of strategies of spatiotemporal summations. Although CFF is unrivaled to quantify the ability of an organism to track a moving object, whether it is representative of other sensory systems is an open question for further investigation. However, as suggested by a few reports (for example in olfaction, Rumbo and Kaissling 1989, Lemon and Getz 1997, Smear et al. 2011, Jacob et al. 2017), temporal resolution might reflect properties common to diverse neural networks rather than specificities of the receptors (Butts et al. 2007, Panzeri et al. 2010) and, hence, be similar in the visual and other sensory systems.

Most of the overall variability results from variations at smaller mass ranges. Within uni- and multi-cellular organisms considered separately, the mass-scaling exponents are not significantly different from zero or result from a small-scale trend (T_L in large metazoans), so that the T_L (small) mass dependency in single cells appears as an exception that will need further data to be interpreted. For T_S and T_L, differences between single cells and metazoans contribute to the overall variability. The twice longer geometric mean of T_L in single cells (Table 1) is well documented (n = 70 species) but the six times longer one of T_S (n = 7) should be confirmed on a larger sample.

Although outside the scope of this paper, we examined narrower mass ranges, i.e. groups of related species of the same class (or kingdom in microorganisms) including more than three species (Fig. S3, S4, S5 and Table S6). For most groups, the mass scaling exponents are positive with intercepts decreasing with mass, so that all the data still lie in a relatively narrow range, as found previously for the mass specific metabolism (Makarieva et al. 2008, Hatton 2019) and its maximum value (Makarieva et al. 2005). For simple response times T_S, the only exponent that reaches statistical significance is that of mammals (Fig. S3) where the trend explains 42% of the variance and agrees with previous studies (section 4.3). Although not significant, the trend in bacteria stands out owing to the proportion of variance it explains (81 %) and its steep slope ($\alpha = 0.66$) which agrees with first-principle derivations (section 5). For the flicker fusion time, the mass exponent of the small-scale regressions are not significantly different from zero. Finally, for the minimum time to move by one body length, the positive mass scaling exponent of mammals stems from large masses (the inflection point near 50 kg is apparent in Fig. 4), as noted and interpreted by Meyer-Vernet and Rospars (2016); we shall return to this point in section 5.

4.2. *Possible Errors Resulting from Biological, Methodological and Experimental Factors*

Are our data and analyses adequate for supporting our conclusion that the simple response time T_S lies within less than a factor of ten from the mean for organisms varying by more than 20 orders of magnitude in mass, as previously shown for the minimum time to move by one body length T_L (Meyer-Vernet and Rospars 2016)? That a similar finding holds for T_F over the smaller 10^8-fold mass range for which this time could be measured? And that these time scales display small or no systematic variation with body mass in uni- and in multicellular organisms? Several criticisms could be raised.

First, one could object that the diversity of organisms, of sensory and motor mechanisms, and of experimental procedures hides any trend in the data. However, it is unlikely that the restriction to more homogeneous data would reveal trends presently hidden because the smaller size of samples would decrease the statistical significance. On the contrary, the diversity of species, measurements and systems is indispensable to estimate reliably the variability and mean of the timescales, independently of the specializations and limitations of taxa and systems. Our aim is to transcend mass scalings holding within groups by considering large ranges of mass and taxonomic groups.

Second, the evolution of different traits is correlated throughout a phylogenetic lineage so that species values do not represent statistically independent data (Felsenstein 1985). This leads to overestimation of degrees of freedom, which artificially narrows confidence intervals. Our major finding that timescales lie within close bounds and that for unicellular (for T_S) and multicellular organisms (for all timescales) they do not significantly depend on mass would not be adversely affected by any widening of confidence intervals (on the contrary for T_L in single cells) and is therefore impervious to this criticism.

A third possible objection is that several experimental factors affecting the measurements have not been considered explicitly. The electrical or behavioural measurement methods play a minor role and correcting them would have practically no effect (Fig. S2 and Table S10 show that their difference is not significant). However, the effect of temperature, which is an important determinant of metabolism and behaviour, should be checked. We thus studied how correcting the time scales of ectotherms to a standard temperature $\theta_0 = 20$ °C would change our results (see Methods). First, the temperature being unknown in several measurements, we considered the worst-case scenario assuming that short time scales ($T < \mu^*$) were measured at 10 °C, and would thus be still shorter if they had been measured at θ_0, and that long time scales ($T \geq \mu^*$) were measured at 30 °C, these two temperatures being close to the extremes in our data (Fig. S7A). For this preliminary test, we used the mean activation energy $E = 0.66$ eV observed in a wide range of species and traits (Dell et al. 2001), and studied how the percentage of timescales lying outside the range [$\mu^*/10$, $\mu^* \times 10$] would be affected by temperature in this worst-case scenario. For all timescales, this percentage is less than 3 % without standardization (Table S11a) and less than 10 % with standardization (Table S11b), except for T_S where it is 5 % and 22 % respectively. Next, noting the greater sensitivity of T_S, we applied a finer standardization procedure to this timescale, for which the temperature is known in 72 % of our data for ectothermic species, based on the different mean activation energies of movements away from and toward a stimulus (see Methods). This procedure leads to no significant change neither in the distribution of T_S values (Fig. S7B) nor in the number of species beyond the limits (it remains the same, i. e. four, Fig. S7). This indicates that our results in mean, variability and overall trend are robust with respect to temperature.

4.3. *Comparison with Previous Work*

Several studies across a wide range of mass and life forms have found organisms' properties to lie in a relatively narrow range, without mass scaling across groups, despite the size scaling observed within groups. This is the case for the mass-specific metabolic rate (Makarieva et al. 2008, Hatton et al. 2019), its maximum value per unit of active mass (Makarieva et al. 2005), the cross-section-specific forces exerted by muscles and molecular motors (Marden and Allen 2002, Marden 2005, Rospars and Meyer-Vernet 2016), and the minimum time to move by one body length $T_L = L/V_{max}$ (McMahon and Bonner 1983, Meyer-Vernet and Rospars 2015, 2016).

However, for the simple response time T_S and the critical flicker fusion time T_F, previous studies concern only relatively small mass ranges and we have included these data. The mass scaling of sensorimotor delays has been studied by More and Donelan (2018) in the particular case of the stretch reflex − a monosynaptic reflex that governs the fastest neural response to peripheral stimuli in terrestrial mammals, with a determination of the different components and a comparison with stance and stride durations. In our T_S sample, we have used the sum of these components except the force generation delay (time between force onset and peak), in coherence with the rest of our data, for which the response is measured by the onset of force production or the onset of movement (which can begin before the production of peak force). These data points lie within the range of our general data set T_S for multicellular organisms, where the nerve conduction delay is expected to be mainly responsible for the increase of T_S shown in figure 2 at large mass. Indeed, the increase in nerve conduction speed due to increase in fibre diameter and to myelination is too moderate to compensate for the increase in distance of conduction, because of the trade-off between responsiveness and compactness (Castelfranco and Hartline 2016), resolution (More et al. 2013), and energy cost (Perge et al. 2012). Let us compare the nerve conduction delay estimated by More and Donelan (2018) $T_{cond} = 5.3\ M^{0.3}$ ms to the geometric

mean (T_S = 22 ms) that we find for multicellular species (Table 1). This yields $T_{cond}/T_S = 0.24\ M^{0.3}$, which shows that the conduction delay becomes important only for large M, although even for the largest mammal studied (the elephant), T_S is only four times larger than its average value.

5. QUANTITATIVE INTERPRETATIONS FROM FIRST PRINCIPLES

The variation of the simple response time, as well as the other time scales studied here, by less than a factor of ten around their mean for organisms so diverse in structure and size suggests that it may be determined by basic constraints set by the universal properties of living matter. We will thus derive first-principle estimates, trying to capture the essential processes at play, whereas neglecting specific details that should be considered in scaling studies over narrow ranges of mass and taxa. Such simple analytic calculations are expected to yield only order-of-magnitude results, that is to within a 10-fold or so accuracy, similar to the variability of the time scales in our data, in the line of the so-called "Fermi problems" or of Weisskopf's physics courses (Weisskopf 1975, 1989).

5.1. *Simple Response Time*

Consider first the simple response time T_S of microorganisms. It includes the transmission delay from the sensor(s) receiving external stimuli to the motor apparatus producing the response by regulating the swimming behaviour. A basic process is the transport of a signalling molecule through the cytoplasm (e.g. Bitbol and Wingreen 2015) via diffusion (e.g., Purcell 1977, Dusenberry 2009). In water, of viscosity $\eta \simeq 10^{-3}$ kg m^{-1} s^{-1}, a sphere of diameter d at

temperature θ has a diffusion coefficient $D = k_B\,\theta/(3\pi\eta\,d)$, where k_B is Boltzmann constant. Signalling molecules are small proteins of typical size $d \simeq 3$ nm, like the key signalling protein CheY (Bren and Eisenbach 2000), yielding a diffusion coefficient in water $D \simeq 150$ μm²/s. Assuming that the crowding of the cytoplasm decreases D by one order of magnitude (e.g. Dill et al. 2011, Mika and Poolman 2011) and that the sensor-to-motor distance equals the organism's length L, we find the three-dimensional diffusion time $L^2/6D$

$$\tau_{dif} \simeq 10\, L_{\mu m}{}^2 \text{ ms}. \quad (1)$$

This timescale is the minimum response time T_S of a microorganism of size L if information is transmitted through the cytoplasm by diffusion of signalling proteins, which is the most basic process. With $L \propto M^{1/3}$, this would yield a mass variation $T_S \propto M^{2/3}$, as observed for bacteria (see the leftmost regression line in Figure S3 with slope α = 0.66, as given in Table S5). The median mass of a bacterium of length L being $M \simeq (3.3L)^3$ (Meyer-Vernet and Rospars 2016), the length of a bacterium of mass 10^{-15} kg (μ_M*, Table S6) is $L \simeq 3$ μm. We deduce from Eq. (1) $T_S = 90$ ms, which agrees to better than a factor of two with the empirical value for bacteria (μ* = 144 ms in Table S5) and is close to the response time given by their regression line ($T_S = 100$ ms for $M = 10^{-15}$ kg, Table S6).

Consider now multicellular organisms. For most of them, the responses are mediated by conduction of information via electric pulses propagating through neurons, whose membrane regulates the permeation of ions via an insulating lipid bilayer and proteins. The proteins act as active ion channels and pumps and the lipid bilayer acts as a capacitance that enables charges to accumulate and produce a potential across it. Biological membranes are also involved in sense organs, via the concentration gradients they enable which produce active transport, whereas ion channels play an essential role in signal transduction (Martinac and Cox 2016). The role of ions

to alter charge and thus protein conformation is essential in signal transduction in both uni- and multicellular organisms (Clapham 2007). For example, paramecia use Ca^{2+} ions and show dynamic changes in the electrical properties of their membrane in response to stimuli, as do neurons, and the structures of their receptors are similar to those of vertebrates (e.g. Maegawa 2017).

A tentative first principle estimate of T_S can be obtained from the inverse of the number of action potentials sent along an axon per second, since this is the shortest possible time to send a bit of information along an axon. Let us first evaluate the cost of generating an action potential U per surface S of membrane, of width a and dielectric constant ε_m, so that the capacitance is

$$C \simeq \varepsilon_0 \, \varepsilon_m \, S/a, \tag{2}$$

where ε_0 is vacuum permittivity. With the electric charge across the membrane CU, of energy CU^2, the cost of an action potential is obtained from (2) as $\varepsilon_0 \, \varepsilon_m \, S \, U^2/a$, which agrees with values in the literature (Aiello 2000). Using two biological properties common to living matter: the mass density $\rho \simeq 10^3$ kg/m^3 and the maximum metabolic rate per unit mass of active tissue $b_M \simeq 2\times10^3$ W/kg (Makarieva et al. 2005), the maximum power available to this surface S of membrane of mass $\rho a S$ is

$$b_M \rho a S \tag{3}$$

Dividing this maximum power by the cost of an action potential estimated above and using the energy corresponding to one monovalent ion crossing the membrane $eU \simeq W_0$, where $e = 1.6\times10^{-19}$ C is the electron charge and W_0 is the energy released by one ATP molecule, we deduce the maximum number of action potentials per unit time, whose inverse yields

$$T_S \simeq \varepsilon_0 \varepsilon_m W_0^2/(\rho b_M e^2 a^2) \tag{4}$$

Substituting the typical dielectric constant of lipids $\varepsilon_m \simeq 2$, a membrane width $a \simeq 6$ nm – similar to the typical protein size (e.g. Erickson 2009), the above value of b_M, and the first-principles relation (Meyer-Vernet and Rospars 2016)

$$W_0 \simeq e^2/(4\pi\varepsilon_0 a) \quad (5)$$

we obtain $T_S \simeq 14$ ms, close to the empirical mean simple response time T_S of metazoans (22 ms).

5.2. *Flicker Fusion Time*

Let us now estimate the timescale T_F, assuming that it is limited by the membrane time constant τ_m. For a surface S of membrane of width a and resistivity r_m, the electrical resistance is $R = r_m\, a/S$ and the capacitance is given by (2), so that the time constant $\tau_m = RC$ is given by

$$\tau_m = r_m\, \varepsilon_0\, \varepsilon_m. \quad (6)$$

To estimate a basic value for the resistivity r_m, independent on the details of the system, we consider again energy constraints. In an electrical circuit of resistance R, submitted to the potential difference U, the power is U^2/R. Using the maximum power available (3), we deduce the resistance $R \simeq U^2/(b_M \rho\, a\, S)$, whence the resistivity $r_m \simeq U^2/(\rho b_M\, a^2)$. Using again the order of magnitude $U \simeq W_0/e$, we deduce τ_m, which yields the flicker fusion time $T_F \simeq \tau_m$ (reflecting the ability of the membrane to resolve a time-varying signal)

$$T_F \simeq \varepsilon_0 \varepsilon_m W_0^2/(\rho b_M\, e^2 a^2) \simeq T_S \simeq 14 \text{ ms} \quad (7)$$

close to the empirical value of T_F (25 ms), and in agreement with our empirical result $T_F \simeq T_S$. The absence of significant increase of T_F for the largest masses (Fig. 3), contrary to what is

observed for T_S (Fig. 2) suggests that the signal conduction time and hence the organism length L plays a minor role in $T_{F,}$ contrary to T_S.

5.3. *Minimum Locomotion Time*

An order of magnitude estimate of the minimum time to move by one body length $T_L = L/V_{max}$ was derived by Meyer-Vernet and Rospars (2016) from the invariance over the whole domain of life of the force per cross-sectional area exerted by molecular motors and muscles ($f \simeq W_0/a^3 \simeq 2\times10^5$ N/m², Rospars and Meyer-Vernet 2016), and the two basic quantities considered above, mass density ρ and mass-specific (per unit mass of active tissue) metabolic rate at maximum activity b_M. The maximum speed was estimated as $V_{max} \simeq L\,\rho\,b_M\,/\,f$ for swimming and running organisms (including microorganisms) of length L satisfying $L \lesssim (f/\rho)^{3/2}/b_M \simeq 1.4$ m − corresponding roughly to $M \simeq 50$ kg (Meyer-Vernet and Rospars 2016). This yields $T_L \simeq L/V_{max}$, the minimum time to move by L

$$T_L \simeq f/(\rho\, b_M) \simeq W_0/(\rho\, b_M\, a^3) \simeq 100 \text{ ms} \quad (8)$$

for $M \lesssim 50$ kg, which agrees to better than a factor of two with the empirical value (59 ms, geometric mean of T_L for all organisms of mass $M < 50$ kg, Table 1). The increase in T_L observed for larger organisms (Fig. 4) has been interpreted by dynamic constraints, yielding

$$T_L \simeq L\,(\rho/f)^{1/2} \quad (9)$$

(Meyer-Vernet and Rospars 2016), in agreement with the known maximum speed of about 15 m/s (e.g. McMahon and Bonner 1983, Garland, 1983, Iriarte-Diaz 2002).

It is interesting to note that our estimates of the minimum times for response (4), for vision (7), and for moving by one body length (8) all yield timescales proportional to the inverse of the

maximum mass-specific metabolic rate (per unit of active mass). This suggests that, since the metabolic rate varies with mass within groups of related species, these time scales may depend not only on body mass within groups of related species but also on metabolic rates. This is shown for T_L in mammals (Fig. S6B), which is inversely proportional to the maximum mass-specific metabolic rate, as expected from (8) if the proportion of active tissue in the body mass does not vary in the range considered in the regression.

Finally, it is noteworthy that Eqs. (4), (5) and (8) yield $T_L/T_S \simeq 4\pi/\varepsilon_m \simeq 6$ in order of magnitude, to be compared to the empirical ratio $T_L/T_S = 78/26 = 3$, suggesting that fast reacting species are also fast moving.

6. CONCLUSIONS

We have shown that across the whole of mobile life, from bacteria to large vertebrates, the simple response time T_S lies in a relatively narrow range, with 95 % of species reacting in a time that differs by less than one order of magnitude from the mean, in striking contrast to the 20 orders of magnitude difference in body mass. The simple response time does not display significant scaling with body mass across groups in unicellular organisms nor in multicellular ones, although it is almost six times larger in the former life form. The absence of large-scale trend does not preclude – and is indeed compatible with various scalings valid in narrower ranges of size and taxa, as is known for the specific metabolic rate. However, within narrow ranges, the detailed characteristics of the organisms must be considered and it is only on larger scales that these variations can be transcended.

This simple response time T_S is close to a well-studied sensory timescale (the inverse of the critical flicker fusion frequency for vision) T_F, and is a few times smaller than the minimum time

to move by one body length T_L, with all time scales lying in a relatively narrow range. Since this narrow range suggests that these time scales may be strongly constrained by physics and basic properties of life, independently of the structure or mass of the organism, we have performed tentative simple estimates of T_S and T_F based on fundamental physicochemical constants and basic properties common to motile organisms.

It is fair to note that the agreement between these simple estimates of minimum time scales (for sensing, for reacting and for moving) and the measurements is only indicative of the dominant constraints in play (e.g. Phillips and Milo 2009), since several mechanisms may be operating in parallel. For example, one tenth of second is in the middle of the range of protein folding time scales, which however spans six orders of magnitude (e.g. Lane and Pande 2013) and close to the maximal turn-over rate of the most abundant enzyme in the biosphere (e.g. Flamholz et al. 2019). The relation $T_S \simeq T_F < T_L$ found from the data (Fig. 1) and tentatively interpreted from first-principles, is reminiscent of symmorphosis (Weibel et al. 1991) and expected to be favoured by evolution since it is indicative of an optimum state. Indeed, if $T_S < T_F$ the sensory resolution would be in excess over motor control whereas if $T_S > T_F$ the response would be limited by sensory performance, so that in both cases, at least one component of the nervous system would be out of tune and wasting energy or space (Laughlin 2001). Likewise, the evolution is expected to favour organisms for which the sensory and response organs act fast enough with respect to their moving performances. It is noteworthy that since the first-principle estimate (8) of T_L holds for both uni- and multi-cellular organisms (Meyer-Vernet and Rospars 2016), the estimate (1) of the minimal response time T_S yields a maximal length L of a few micrometres in order to ensure $T_S \leq T_L$ when the response is mediated by diffusion, as observed for bacteria

These preliminary results encourage further research on the response times of mobile organisms and their fundamental bases. They might also possibly be used to infer properties of extinct species since the reconstructed speed (e.g. Hutchinson and Garcia 2002) and size (e.g. Hutchinson et al. 2011) of the giant dinosaur *Tyrannosaurus rex* yield a time to move by one body length $T_L \simeq 1$ s for a mass $M \simeq 10^4$ kg, which is close to the value expected from (9) and would put *Tyrannosaurus rex* in the middle of the data of extent animals of this size in figure 4.

Ethical Statement

The present article is based on a meta-analysis. No live animals were used.

Data Accessibility

The datasets supporting the article are included in the Supplementary Material.

Competing Interests

We have no competing interests.

Author's Contributions

J.-P.R. and N.M.-V. each made significant and substantial contributions to this study in terms of the conception, design, data collection and interpretation of results, as well as preparing the manuscript. J.-P.R. contributed primarily to the statistical analyses and N.M.-V. to the physical analyses.

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TABLE 1. Summary statistics of timescales (in ms) for unicellular, multicellular and all species

Timescale	n	min	max	$Q_{2.5}$	$Q_{97.5}$	r_{95}	δT_{95}	med	IQR	μ^*	s^*	out_{95}	out_{10}
T_S all	81	2.5	485	4.7	311	66	1.82	24	43	26	3.26	4	4
T_S unicell	7	18.0	350	18.0	350	19	1.29	200	195	129	3.17	0	0
T_S multicell	74	2.5	485	4.7	238	51	1.71	23	35	22	2.93	4	3
T_S multic<50kg	68	2.5	240	4.6	148	32	1.51	18	28	19	2.64	4	1
T_F all multic	106	2.5	250	4.2	100	24	1.37	24	27	25	2.14	5	1
T_L all	427	5.3	2778	20.9	706	34	1.53	71	99	78	2.73	22	11
T_L unicell	70	5.3	2778	11.9	2778	234	2.37	123	213	145	3.86	2	9
T_L multicell	357	12.5	2525	22.3	567	25	1.41	61	82	69	2.40	18	3
T_L multic<50kg	300	12.5	657	21.5	408	19	1.28	50	61	59	2.22	14	3

Rows: T_S, simple response time; T_F, flicker fusion time; T_L, minimum time to move by one body length.

Columns: n, number of species; minimum; maximum; $Q_{2.5}$, percentile 2.5 %; $Q_{97.5}$, percentile 97.5 %; r_{95}, ratio $Q_{97.5}/Q_{2.5}$ including 95 % values; $\delta T_{95} = \log_{10}(r_{25})$; med, median; IQR, interquartile range; μ^*, geometric mean (ms); s^*, multiplicative standard deviation; out_{95}, number of values outside $[Q_{2.5}, Q_{97.5}]$; out_{10}, number of values outside $[\mu^*/10, \mu^* \times 10]$.

TABLE 2. Dependence of timescales on body mass for unicellular, multicellular and all species

	n	$\log_{10}T_0$	α	IC_1	IC_2	μ_M*	δM	r_α	δT_α	r^2	P	Sig
T_S all	81	-1.69	-0.033	-0.06	-0.01	-3.10	19.59	0.2	-0.64	7	0.02	1
T_S unicell	7	-0.35	0.038	-0.41	0.49	-14.17	3.70	1.4	0.14	1	0.83	0
T_S multicell	74	-1.58	0.036	-0.01	0.08	-2.05	12.11	2.7	0.44	3	0.12	0
T_S multic<50kg	68	-1.77	-0.024	-0.08	0.03	-2.45	9.89	0.6	-0.24	1	0.36	0
T_F all multic	106	-1.57	0.023	-0.01	0.06	-1.93	8.25	1.6	0.19	2	0.19	0
T_L all	427	-1.13	-0.010	-0.02	-0.00	-2.86	21.05	0.6	-0.20	1	0.03	1
T_L unicell	70	0.10	0.078	0.02	0.14	-12.01	8.01	4.2	0.63	10	0.01	1
T_L multicel	357	-1.11	0.044	0.03	0.06	-1.06	14.15	4.2	0.62	7	0.00	1
TL multic<50kg	300	-1.25	-0.010	-0.03	0.01	-1.72	10.70	0.8	-0.10	0	0.34	0

Rows: same as in Table 1.

Columns: n, number of species; $\log_{10}T_0$, intercept of least square regression line, $\log_{10}T = \log_{10}T_0 + \alpha \log_{10}M$; α, allometric coefficient; [IC_1, IC_2], 95% confidence intervals of slope α; μ_M*, mean $\log_{10}M$; δM, mass range of the category, $\delta M = \log_{10}(M_{max}/M_{min})$, with M_{max} and M_{min} masses of heaviest and lightest species in the category; r_α, fitted ratio T_{max}/T_{min} with $T_{max} = T_0(M_{max})^\alpha$ and $T_{min} = T_0(M_{min})^\alpha$; $\delta T_\alpha = \log_{10} r_\alpha$; r^2, coefficient of determination (percent); P, p-value of test of slope $\alpha = 0$; Sig, slope α of regression line significantly different from zero (1) or not (0).

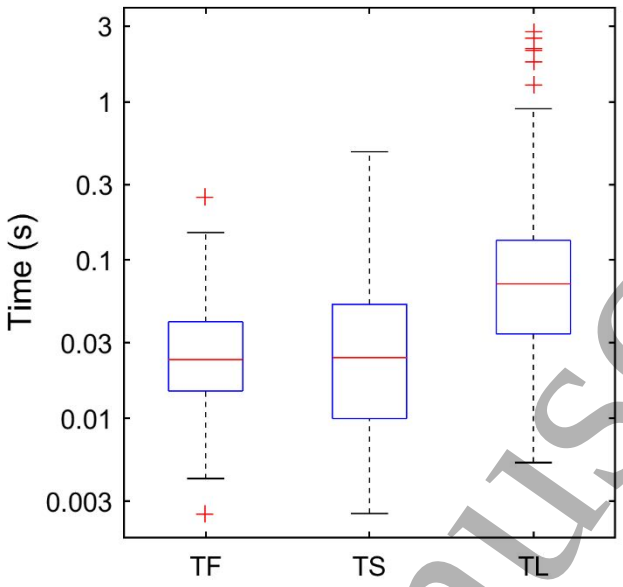

Figure 1. Boxplots of log-transformed flicker fusion times T_F, simple response times T_S, and times to move by one body length at maximum speed T_L. The boxes extend from the lower quartile to the upper quartile values with the medians (red line) in between. The whiskers extend to the most extreme data values within 1.5×IQR. Outliers (red crosses) are values beyond the end of the upper whiskers. ANOVA and multiple comparisons of means (Supplementary material, Table S7): $T_F = T_S \neq T_L$.

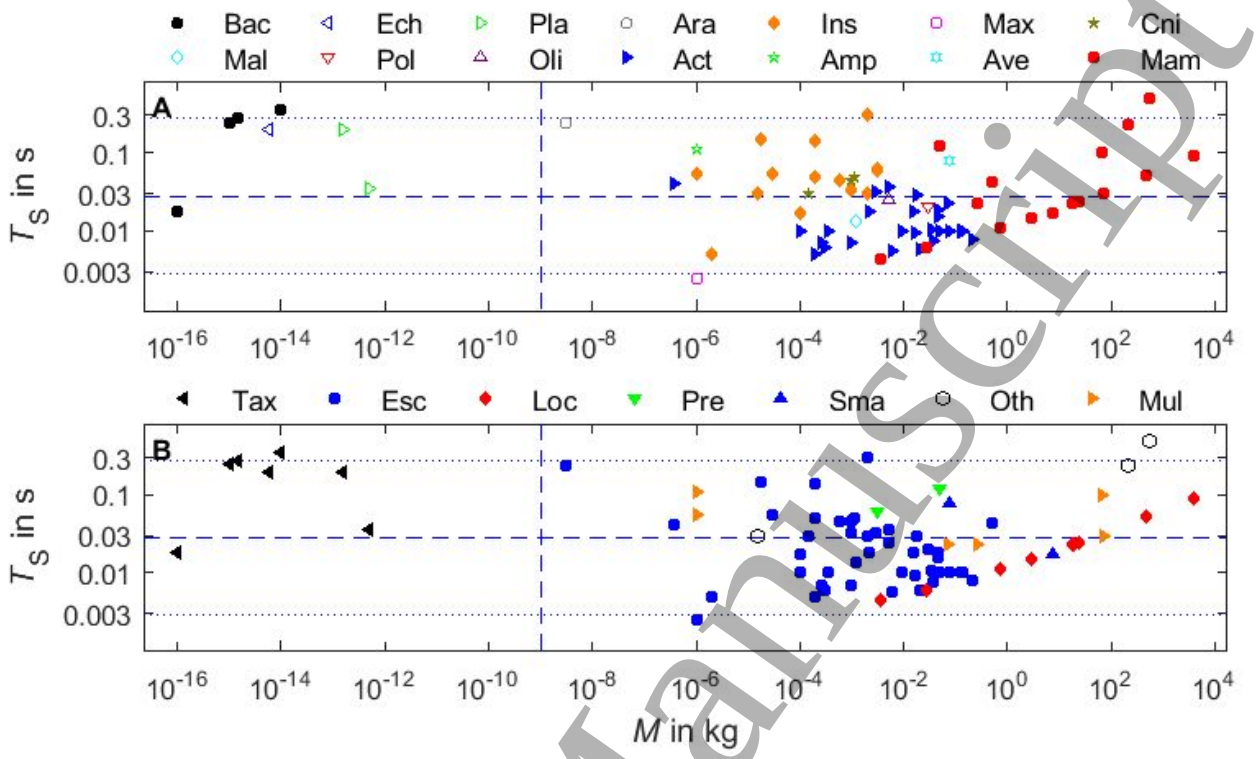

Figure 2. Simple response times T_S versus cell or body mass M (n = 81). For clarity, the scale on the y-axis is 1.5 times larger than on the x-axis .

A. Taxonomic groups. Groups with three species or less shown as empty symbols, other groups as filled symbols. Bacteria (Bac, n = 4), Echinodermata (Ech, 1, sperm), Planta (Pla, 2), Arachnida (Ara, 1), Insecta (Ins, 16), Hexanauplia (Hex, 1; copepods), Cnidaria (Cni, 3), Malacostraca (Mal, 2; crustaceans), Polychaeta (Pol, 1; bristle annelids), Oligochaeta (Oli, 1; earthworms), Actinopterygii (Act, 28; cartilaginous fishes), Amphibia (Amp, 1), Aves (Ave, 1; birds), Mammalia (Mam, 18). The horizontal dashed line is the geometric mean μ^* (26 ms) with values larger and smaller by one order of magnitude dotted. Vertical dashed line separates unicellular from multicellular organisms. Intermediate-scale regression laws for, from left to right, single cells (solid black line), multicellular organisms above 50 kg excluded (dashed black line) and included (solid black line). Slopes not significantly different from zero.

B. Types of response. Species tested for a single type of response shown in filled symbols: cell chemotaxis and phototaxis (Tax, n = 7), startle with escape (Esc, 46), sensory control of locomotion (Loc, 11), predatory movement (Pre, 6), small movement in startle of birds and mammals (Sma, 2), other behaviour (Oth, 3; see Table S1). Species tested for two or more types of response (empty symbol, Mul, 6). Dashed and dotted horizontal lines as in A.

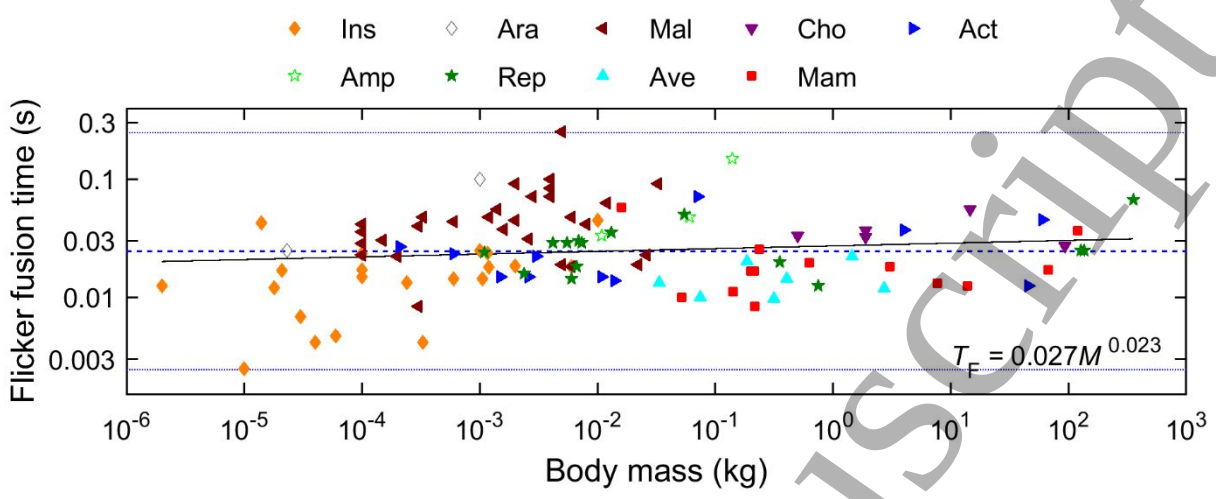

Figure 3. Flicker fusion times T_F versus body mass M (n = 106) according to taxonomic groups, shown as colour of empty and filled symbols as in Fig. 2. Arachnida (Ara, n = 2), Insecta (Ins, 21), Malacostraca (Mal, 29; crustaceans), Cho (Chondrichthyes, 5; cartilaginous fishes), Actinopterygii (Act, 11; ray-finned fishes), Amphibia (Amp, 3), Reptilia (Rep, 15), Aves (Ave, 7; birds), Mammalia (Mam, 13). The horizontal dashed line is the geometric mean μ^* (25 ms) with values larger and smaller by one order of magnitude dotted. Scaling regression law in inset. Slope not significantly different from zero.

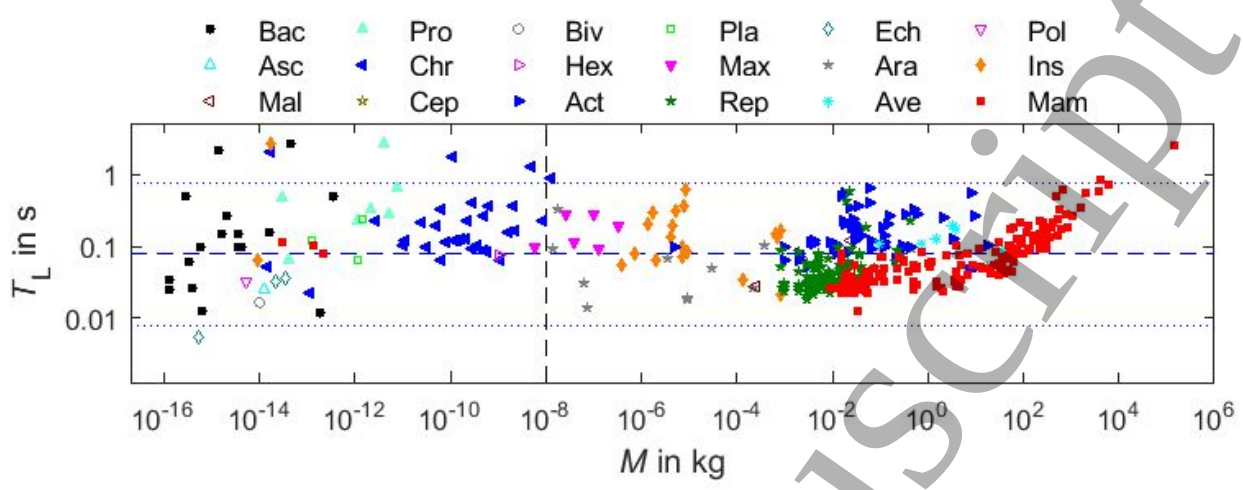

Figure 4. Times to move by one body length at maximum speed T_L versus cell or body mass (n = 426) according to taxonomic groups. For clarity, the scale on the y-axis is 1.5 times larger than on the x-axis. Groups with three species or less shown as empty symbols, other groups as filled symbols. Bacteria (Bac, n = 17), Protozoa (Pro, 7; flagellates), Bivalvia (Biv, 1, sperm), Planta (Pla, 3), Echinodermata (Ech, 3, sperm), Polychaeta (Pol, 1, sperm; bristle annelids), Ascidiacea (Asc, 1, sperm; sea squirts), Chromista (Chr, 32; ciliates), Hexanauplia (Hex, 6; copepods), Arachnida (Ara, 10), Insecta (Ins, 20; 2 sperm), Malacostraca (Mal, 3; crustaceans), Cephalopoda (Cep, 1), Actinopterygii (Act, 55; cartilaginous fishes), Reptilia (Rep, 96), Aves (Ave, 9; birds), Mammalia (Mam, 161; 3 sperm). The horizontal dashed line is the geometric mean μ* (78 ms) with values larger and smaller by one order of magnitude dotted. Vertical dashed line approximately separates unicellular and multicellular organisms. Intermediate-scale regression laws in inset as in Fig. 2. Slopes significantly different from zero, except for multicellular organisms under 50 kg.