doi:10.1111/j.1558-5646.2009.00639.x

EVOLUTION OF MAMMAL TOOTH PATTERNS: NEW INSIGHTS FROM A DEVELOPMENTAL PREDICTION MODEL

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Received August 11, 2008
Accepted December 17, 2008

The study of mammalian evolution is often based on insights into the evolution of teeth. Developmental studies may attempt to address the mechanisms that guide evolutionary changes. One example is the new developmental model proposed by Kavanagh et al. (2007), which provides a high-level testable model to predict mammalian tooth evolution. It is constructed on an inhibitory cascade model based on a dynamic balance of activators and inhibitors, regulating differences in molar size along the lower dental row. Nevertheless, molar sizes in some mammals differ from this inhibitory cascade model, in particular in voles. The aim of this study is to point out arvicoline and murine differences within this model and to suggest an alternative model. Here we demonstrate that the inhibitory cascade is not followed, due to the arvicoline's greatly elongated first lower molar. We broaden the scope of the macroevolutionary model by projecting a time scale onto the developmental model. We demonstrate that arvicoline evolution is rather characterized by a large gap from the oldest vole to more recent genera, with the rapid acquisition of a large first lower molar contemporaneous to their radiation. Our study provides alternative evolutionary hypotheses for mammals with different trajectories of development.

KEY WORDS: **Arvicolinae, evo-devo, evolution, inhibitory cascade, rodents.**

Recent mammalian biodiversity is a consequence of complex life-history evolution influenced by dynamic, biotic, or abiotic phenomena. Palaeontologists have usually considered mammalian evolutionary patterns from morphological trait variations (e.g., Hunter and Jernvall 1995; Line 2003; Polly 2005; Evans et al. 2007; Plavcan and Ruff 2008) in relation to environmental changes to interpret adaptive radiations, for instance. However, phenotypic and genetic processes leading to mammal morphological changes are often suggested but rarely demonstrated. Hence, one objective of developmental biology studies is to contemplate

developmental mechanisms that may influence these evolutionary changes (Salazar-Ciudad and Jernvall 2004).

A new model established from murine dental development has recently been proposed to predict evolutionary patterns in lower mammalian teeth (Kavanagh et al. 2007). By using tooth germ culture and by cutting the posterior tail that forms the second lower molar (*m*2) from the first lower molar (*m*1), Kavanagh and colleagues demonstrated that the *m*2 arose significantly earlier and increased in size. In addition, induction of mesenchymal activators (*Bmp4* and *activin* βA; signaling molecules which activate tooth development) significantly accelerated the formation of *m*2 without cutting it from the *m*1. Then, they deduced that the timing of the initiation of the posterior molars depends on previous molars through a dynamic balance between intermolar inhibition and mesenchymal activation.

Consequently, this model is constructed as an inhibitory cascade model (IC model) based on the dynamic balance between inhibitors (*i*) and activators (*a*), defined by the *a*/*i* ratio. They underlined that changes in the *a*/*i* ratio produce modifications in molar tooth proportions and lead to different dental phenotypes between *m*1, *m*2, and third lower molar (*m*3). Moreover, low *a*/*i* leads to a relatively larger first lower molar, whereas high *a*/*i* results in more equal molar sizes, and if *a*/*i* is very high (above 1.0), the posterior molars will be larger. Extrapolation of the IC model allows *a*/*i* to be estimated from molar proportions in extant and particularly in fossil species (Polly 2007), helping to infer evolutionary processes in different taxa at a macroevolutionary scale. However, some taxa do not fit their model (bears, horses, and voles).

Voles, in particular, are not consistent with the model due to their oversized first lower molar (*m*1) compared with *m*2 and *m*3 size (Kavanagh et al. 2007). Contrary to murines**,** voles are characterized by hypsodont prismatic molars formed by enamel triangles. The number of triangles can be variable between vole genera. Cement is present inside the reentrant angles of the triangles. These are reasons why vole molars have increasingly been used as a parallel model to improve our knowledge of rodent cheek tooth development (e.g., Keränen et al. 1998; Jernvall et al. 2000a; Salazar-Ciudad and Jernvall 2002; Matalova et al. 2005; Witter et al. 2005; Setkova et al. 2006). Furthermore, voles are considered, among terrestrial mammals, as good models to study evolutionary mechanisms and they account for one of the most widely diversified mammal groups of the Quaternary (Chaline 1972; Chaline and Mein 1979; van Kolfschoten 1990; Fejfar and Repenning 1992; Nadachowski 1992; von Koenigswald 1992; van Kolfschoten 1992; Sesé 1995; Montuire and Desclaux 1997; Montuire et al. 1997; Montuire 1999; Montuire and Marcolini 2002).

The aim of our study is to characterize the peculiarity of arvicoline lower molars (voles and lemmings) within the IC model framework and define another model based on molar areas. Can we better understand the vole and lemming developmental distinctiveness if we compare them to murines using this IC model? Given that differences are noticeable, what hypotheses can be suggested to explain the divergence in the vole dental trajectory?

Recently, dental phenotypic variability has been investigated with character measurements on both extant and fossil populations to detect the causal effects leading to arvicoline diversification (Nadachowski 1984; Marchand et al. 2003; Montuire and Brunet-Lecomte 2004; Nappi et al. 2006). We project arvicoline fossil data onto the developmental model of Kavanagh et al. (2007). Indeed, a recent study insists on the necessity of a time scale in evolutionary developmental biology (Raff 2007). Thereby, we can explore a real macroevolutionary trend through time within vole and lemming molar ratios to emphasize evidence of past developmental features in the arvicoline radiation.

Materials and Methods

EXTANT AND FOSSIL LOWER DENTAL ROW SPECIMENS

Photographs and drawings of scaled lower dental rows from extant and fossil arvicoline individuals (voles and lemmings) were compiled from both literature and rodent collections stored at the University of Burgundy and International Campus of Baillarguet (France, see Supporting Information). All tribes defined in voles and lemmings from Eurasia and North America are represented (McKenna and Bell 1997). Twenty genera of arvicoline rodents covering a wide spectrum of morphological variability in each tribe were considered. All individuals were classed into two groups: (1) 14 genera of fossil individuals, (2) eight genera of extant individuals. Data for mice are from Kavanagh et al. (2007) supporting information. Extant and fossil cricetines are considered as the ancestral tooth pattern for arvicoline and murine molars (Hartenberger 1998; Fejfar 1999; Kälin 1999). They were obtained by our measurements from literature illustrations of scaled lower dental rows and rodent collections of the National Museum of Natural History in Paris (France).

For extant vole specimens, an attempt was made to measure 30 individuals per genus. For fossil vole specimens, the entire lower dental row is rarely preserved, however, a few individuals were nonetheless available (1 to 9; see Supporting Information). Our dataset for arvicolines consists of more than 230 area measurements of complete lower dental rows (see Supporting Information).

METHODS

Lower molar size is estimated using the area of the occlusal surface. Two different proxies can be used to measure tooth area: (1) length by width or (2) outline surfaces. In arvicolines, these two

measurement proxies have been tested. Because of their complex and prismatic outline, the area measurements between the two proxies are significantly different (nonparametric Wilcoxon test, normal approximation: $z = 4.096$, $P = 4.1 \times 10^{-5}$). The length by width overestimates the area calculation. Therefore, the outline surface measurements were used in this study.

To compare our vole data with murine area measurements obtained by Kavanagh et al. (2007), we used the same software, Image J (http://rsb.info.nih.gov/ij/), to measure the occlusal surface area. The number of pixels within the tooth outline was calculated by the software. We used drawings of vole teeth from camera lucida because Image J does not automatically extract the outline of the molars directly from pictures.

The IC model examines how lower molar initiation and size in the mouse are regulated along the dental row. The lower molar teeth develop from the anterior to the posterior of the dental row. The activation–inhibition balance leads to equal-sized molars, whereas increasing inhibition has a cumulative effect from the second to the third molar. Relative lower molar size consequently reflects this inhibitory cascade throughout molars following the equation:

$$Y = 1 + [(a - i)/i](X - 1),$$

where Y is molar size relative to its position; X is molar position (e.g., 1, 2, 3 . . .), a is activator, and i is inhibitor.

The $(a - i)/i$ represents the relative strengths of the activators versus the inhibitors.

The above equation gives, for molar areas, $m1 = 1$; $m2 = a/i$ and $m3 = 2a/i - 1$. The relationship between the molar proportions ($m2/m1$ vs. $m3/m1$) is $m3/m1 = 2\ (m2/m1) - 1$. Thus, $m2/m1$ versus $m3/m1$ demonstrates the inhibitory cascade along the tooth row. For mammals with three molars, applying the a/i ratio, $m2$ will be one-third of the total molar area ($m1 + m2 + m3$). Moreover, high a/i leads to equal lower molar size, whereas low a/i results in a relatively larger first lower molar.

In the case of simple linear regression, several approaches may be used: least-square adjustment, major axis, and reduced major axis. For comparisons with Kavanagh et al.'s results, the relationships between molar ratios are plotted with PAST version 1.71 (Hammer et al. 2001), using reduced major axis (Model II regression, for $m2/m1$ vs. $m3/m1$ and for $m2$ vs. $[m1 + m2 + m3]$). In the Model II regression line, only the Pearson correlation coefficient "r" is calculated and tested against nullity. In fact, the determination coefficient "R^2" is only the squared-value of "r" and does not provide further information (e.g., about the amount of explained variance, as in a least-square model; G. Escarguel, pers. comm. 2008).

The inhibitory cascade random model (ICR model), defined by Kavanagh et al. (2007), is here applied on arvicoline data to compare with a model in which the a/i ratio varies along the dental row. Model randomizations and calculations of 10,000 reduced major-axis regressions were performed in a MATLAB function (MathWorks, Inc., Natick, MA). Then, predicted $m3/m1$ ratios are calculated from 10,000 randomized reshuffled (without replacement) $m2/m1$ ratios by the equation:

$$(m3/m1)_{\mathrm{Exp}} = m2/m1 - 1 + (m2/m1)_{\mathrm{Shuf}},$$

where $(m3/m1)_{\mathrm{Exp}}$ is the expected ratio of $m3/m1$, $m2/m1$ is the molar ratio of a given individual, and $(m2/m1)_{\mathrm{Shuf}}$ is the reshuffled $m2/m1$ ratio within individuals.

Different analyses of $m2/m1$ versus $m3/m1$ were performed: (1) on extant arvicoline data, to compare with the IC model based on mice and (2) on extant and fossil arvicoline measurements to underline the evolutionary trajectory in molar proportions at the subfamily level.

Results

ARVICOLINE DATA AND THE KAVANAGH ET AL. MODEL

As with the mouse measurements made by Kavanagh et al. (2007), the lower molar proportions of recent arvicolines are included in the same square: $0 \leq m2/m1 \leq 1$ and $0 \leq m3/m1 \leq 1$.

The comparison of the IC model in mouse in Kavanagh et al. (2007) and recent vole and lemming regressions (Fig. 1) demonstrates that the 95% confidence interval (95% CI) of the slope of vole and lemming data is clearly different from the 95% CI of the slope of mouse data (Table 1). A randomization of our arvicoline measurements has been performed by the ICR model (Kavanagh et al. 2007) leading to an average equation with a slope parallel to the murine ICR model equation ($y = 1.413x - 0.668$ for arvicolines; $y = 1.404x - 0.529$ for murines). Furthermore, the mean of the arvicoline slope falls in the 95% CI of the randomized proportions for murines and vice versa (Table 1). The ICR model defined by Kavanagh et al. (2007, see Materials and Methods) represents three categories of lower molar proportions that are predicted by the change of the strength of the inhibition along the dental row: $m1 = m2 > m3$; $m1 \gg m2 > m3$. Most arvicolines fit in the group in which $m1 \gg m2 = m3$, which is close to the $m1 \gg m2 > m3$ predicted by the murine ICR model (Fig. 1). All the lemmings fit in the group in which $m1 > m2 = m3$. Even if the equations of the ICR model for arvicolines (own data) and murines (see Kavanagh et al. 2007) are a mean of all the different regressions generated, not only the slope and intercept values of extant voles and lemmings, but also the 95% CI, are comparable to the ICR models.

In addition, some arvicoline individuals fall within the upper range of the murine distribution (Fig. 1). Two individuals belong to the equal size molars of the murine distribution, and only one extreme arvicoline individual (*Prometheomys schaposchnikowi*)

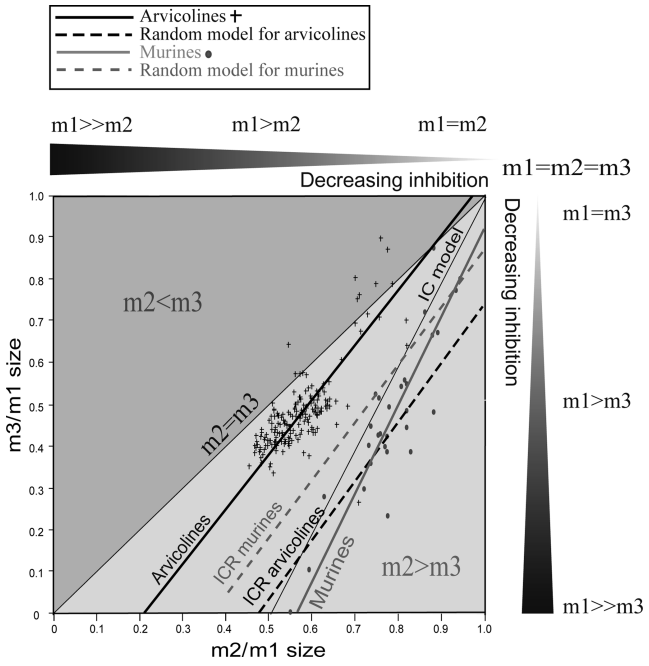

Figure 1. Comparison of extant arvicoline (184 individuals in 12 species) and murine (29 individuals in 29 species) molar proportions in the Kavanagh prediction model. The slope drawn through the extant arvicoline molar sizes (black crosses and line) is 1.389 and the intercept is −0.313 (Table 1). We note the parallelism between arvicoline and random molar prediction regressions (gray dashed line; Kavanagh et al. 2007; black dashed line; this study), whereas arvicoline and murine (gray line) regressions are not parallel. Throughout the murine regression, the decreasing inhibition trajectory provides changes in molar sizes. High inhibition leads to smaller posterior molar. In contrast, low inhibition leads to more equal-sized molar (for more information, see Kavanagh et al. 2007).

has a molar relationship of $m1 > m2 > m3$. For equal molar size murines, only one species (*Hyomys goliath*) falls within in the range of arvicoline molar proportions (Fig. 1).

THE ARVICOLINAE SUBFAMILY

In our extant arvicoline measurements, lower molar proportions in all individuals seem to show a linear regression ($y = 1.389x - 0.313$; Table 1). Most arvicolines (78%) are represented by low values of molar proportions ($m2/m1$ and $m3/m1 < 0.7$) in which the posterior molars $m2$ and $m3$ are much smaller than $m1$: $m1 \gg m2 = m3$ (Fig. 2). Nevertheless some groups of individuals show different molar proportions compared to this general pattern in which $m1 > m2 > m3$ (15%) or $m1 > m2 < m3$ (0.5%, Fig. 2). Another group (Fig. 2), belonging to the *Lemmus* genus, can be distinguished with high molar proportion values ($m2/m1$ and $m3/m1 > 0.70$) in which the molars $m2$ and $m3$ are slightly smaller than $m1$: $m1 > m2 = m3$. An analysis of variance (ANOVA; Model I) and an a posteriori Scheffe's test were performed between all recent arvicoline genera and *Lemmus* was always significantly different from the other genera (for $m2/m1$ and $m3/m1$ $P < 0.001$; Scheffe's test). Consequently, *Lemmus* seems to be different from all other extant arvicolines. Within the arvicolines, one genus, *Prometheomys* (represented by a unique species, *Prometheomys schaposchnikowi*) (Kryštufek and Vohralík 2005; Musser and Carleton 2005) is very far from the general molar proportions ($m2/m1 = 0.70$; $m3/m1 = 0.26$) because of its small $m3$ (Figs. 2, 3). In addition, it is noteworthy that, in the arvicoline macroevolutionary pattern, we observe a change in $m2/m1$ and $m3/m1$ ratios (at about the 0.7 value) between the most frequent scheme with $m1 \gg m2 = m3$ and that with $m1 > m2 = m3$ (Fig. 2).

Table 1. Reduced major-axis regression analysis of arvicoline molar size, arvicoline reduced *m*1 size, and cricetine measurements. The values obtained by Kavanagh et al. (2007) on murines were added for comparisons. Apart from the plot *m*2 versus total dental row area in which regression is based on model I, all the others are based on a model II regression. Only the Pearson coefficient "*r*" is calculated to represent the distribution as "R^2" is only the square of "*r*" and does not indicate the correlation coefficient in a model II regression (see Material and Methods).

Data	Associated figures	Slope	95% CI	Intercept	95% CI	*r*
Extant arvicolines	Fig. 1 and 2	1.390	1.208; 1.555	−0.313	−0.407; −0.213	0.771
Extant murines	Fig. 1 and 2	2.150	1.772; 2.688	−1.219	−1.651; −0.925	0.740
Random model arvicolines	Fig. 1	1.413	1.323; 1.502	−0.668	−0.718; −0.616	0.860
IC model	Fig. 1 and 2	2.00	−; −	0.000	−; −	1.0
Random model murines	Fig. 1	1.404	1.141; 1.673	−0.529	−1.247; −0.584	0.702
Fossil arvicolines	Fig. 2	1.179	0.943; 1.509	−0.233	−0.410; −0.100	0.697
Extant + fossil arvicolines	Fig. 2	1.381	1.219; 1.534	−0.316	−0.403; −0.225	0.750
*m*2 versus total area arvicolines	Fig. 3	3.380	3.308; 3.447	0.325	0.229; 0.421	0.994
*m*2=1/3 total area IC model	Fig. 3	3.000	−; −	0.000	−; −	1.000
Voles	Fig. 5	1.380	1.219; 1.534	−0.316	−0.403; −0.225	0.749
Lemmings	Fig. 5	1.887	0.982; 3.167	−0.623	−1.540; −0.016	0.209
Extant + fossils arvicolines with reduced *m*1	Fig. 6B	1.543	1.191; 1.877	−0.559	−0.814; −0.297	0.787
Cricetines	Fig. 4	1.631	1.191; 2.274	−0.796	−1.393; −0.373	0.876

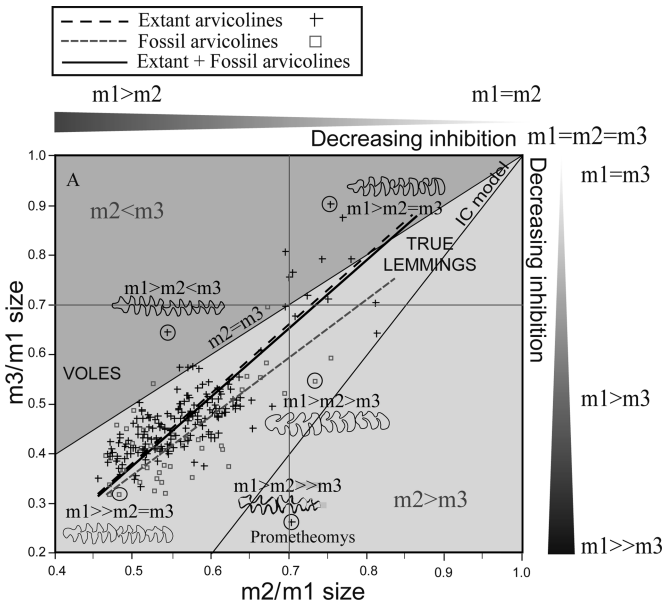

Figure 2. **The arvicolinae subfamily. Extant and fossil molar proportions. The extant and fossil slope regression (1.378; black solid line; Table 1) is more affected by the number of extant data (black crosses and black dashed line: $y = 1.389x - 0.313$; see Table 1) than the fossil data (gray squares and gray dashed line: $y = 1.169x - 0.228$; see Table 1). We observe decreasing inhibition between the majority of arvicolines, with $m1 \gg m2 = m3$, and the other individuals, mostly lemmings, with $m1 > m2 = m3$. True lemming and vole morphological spaces are delimited by perpendicular gray lines. Tooth row drawings illustrate different molar proportions, with their corresponding symbol circled. $m1 \gg m2 = m3$, $m1 > m2 < m3$, $m1 > m2 > m3$, and $m1 > m2 = m3$ represent *Microtus agrestis*, *Lagurus lagurus*, *Clethrionomys glareolus*, and *Lemmus lemmus*, respectively. The outlier of the regression, *Prometheomys schaposchnikowi* ($m1 > m2 \gg m3$), is also represented with a drawing.**

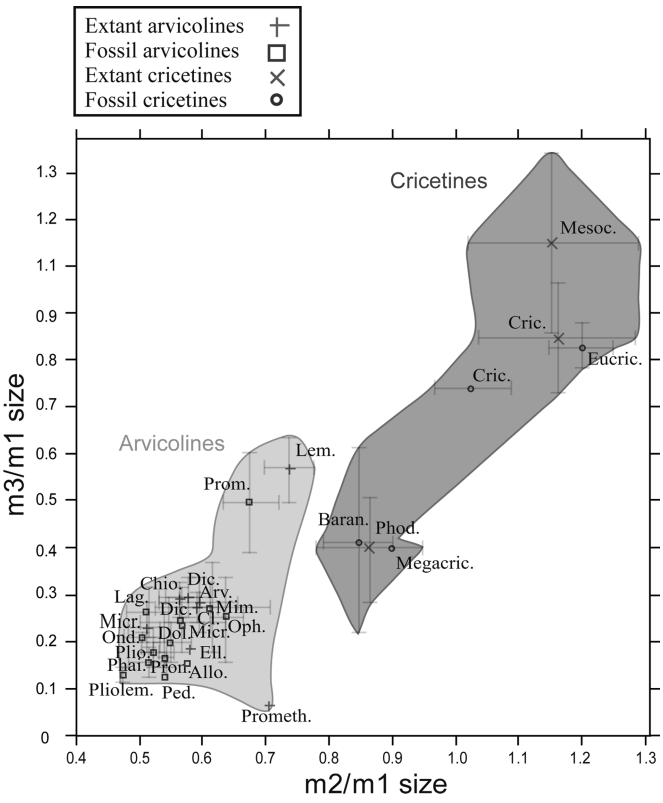

Figure 3. **Means of molar proportions in arvicolines (light gray area) and cricetines (dark gray area), extant and fossil genera. Ancestral molar proportions of cricetines polarize the phenotypic trajectory of arvicolines. Fossil genus abbreviations for arvicolines (black open squares) and cricetines (black open circles): Allo., *Allophaiomys*; Cric., *Cricetus*; Dicro., *Dicrostonyx*; Dol., *Dolomys*; Lag., *Lagurus*; Mesoc., *Mesocricetus*; Micr. *Microtus*; Mim., *Mimomys*; Ond., *Ondatra*; Oph., *Ophiomys*; Ped., *Pedomys*; Phai., *Phaiomys*; Phod., *Phodopus*; Plio., *Pliomys*; Pliolem., *Pliolemmus*; Prom., *Promimomys*; Pron., *Proneofiber*. Extant genus abbreviations for arvicolines (gray crosses) and cricetines (gray diagonal crosses): Arv., *Arvicola*; Chio., *Chionomys*; Cleth., *Clethrionomys*; Cric., *Cricetus*; Dicro., *Dicrostonyx*; Ell., *Ellobius*; Eucric., *Eucricetus*; Lem., *Lemmus*; Megacric., *Megacricetus*; Micr., *Microtus*; Prometh., *Prometheomys*.**

We can also notice that the arvicoline second lower molar is not one-third of total lower molar area, $m2 \neq 1/3\ (m1 + m2 + m3)$ (Fig. 4) contrary to the specific result obtained by the IC model.

THE ARVICOLINAE EVOLUTIONARY PATTERN

We focused our study on the evolutionary pattern of lower molar proportions within the arvicoline subfamily. Kavanagh et al. (2007) did not use fossil data and Polly (2007) did not use this level of organization to study macroevolutionary patterns. Therefore, we added measurements of fossil arvicolines, belonging to extinct and recent tribes, to investigate whether a temporal trajectory can be found in molar proportions within this subfamily. In addition, as cricetines represent an ancestral lineage for arvicolines (Conroy and Cook 1999; Fejfar 1999; Kälin 1999; Steppan et al. 2004), molar proportions of fossil and extant cricetine genera are used to polarize the arvicoline evolutionary trajectory.

Even though we included all the area measurements of fossil arvicolines (14 genera, 47 individuals; Fig. 2 and Table 1), the equation of the general regression (extant and fossil data) was not visibly changed as 95% CI for slope and intercept are overlapping in comparison with the equation obtained from extant data only (Fig. 2 and Table 1). This could, in part, be due to the much greater sample size of the extant compared to the fossil data. As with extant arvicolines, many fossils have low values of molar proportions (i.e., the $m1$ is greater than $m2$ and $m3$), falling off the predicted inhibitory cascade line. All of the proportion values obtained in arvicoline fossils are always lower than the highest values in arvicolines (i.e., *Lemmus*).

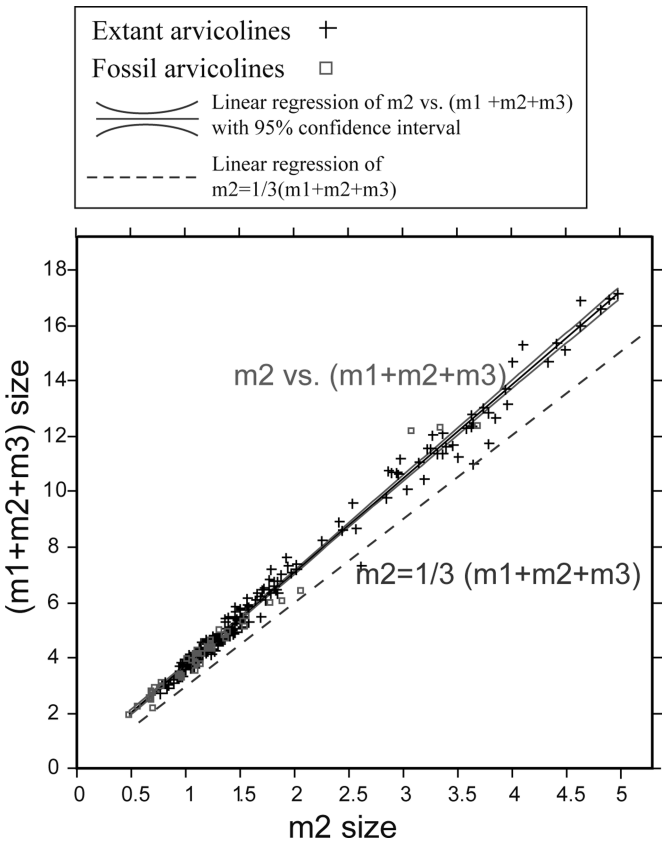

Figure 4. Relation between *m*2 size and total molar area in arvicolines compared with the *m*2 equal one-third of the total molar area predicted by the IC model. The equation ($y = 3.380x + 0.325$; Table 1), based on fossil and extant arvicolines, demonstrates that *m*2 is lower than one-third of the total molar area. The arvicoline *m*2 is too small compared to the IC model. Gray arcs represent the 95% confidence interval.

Figure 3 shows the lower molar proportion mean values of all arvicolines and cricetines to identify the different genera. In this plot, in accordance with the distribution of all individuals (Fig. 2), the majority of the genera are concentrated in the lowermost region of molar proportion values. Not only are *Lemmus* and *Prometheomys* far outside the general distribution of the arvicolines, but so is the fossil genus *Promimomys*, which is the oldest arvicoline found in the Holarctic region (≈ 6–3.8 Ma) (Chaline 1987; McKenna and Bell 1997; Chaline et al. 1999; Kowalski 2001). *Mimomys*, represented by nine individuals, expresses a greater standard deviation than the other arvicoline genera. This genus also represents transitional molar proportions from *Promimomys* to the other fossil and extant arvicolines (Fig. 2). Cricetine lower molar proportions ranged from 0.86 to 1.20 for $m2/m1$ and from 0.60 to 1.25 for $m3/m1$, which are always higher than arvicolines (except for *Lemmus*). Therefore, $m2/m1$ and $m3/m1$ in cricetines can be higher than 1. This means that $m2$ or $m3$ is larger than $m1$: $m1 < m2 = m3$ or $m1 < m2 < m3$. Among cricetines, a large difference is observed between two main groups formed by high values of molar proportions *Mesocricetus*, *Cricetus*, *Eucricetus* ($m2/m1 = 0.93$ to 1.36 and $m3/m1 = 0.89$ to 1.510: $m1 = m2 = m3$) and lower values of molar proportions *Baranomys*, *Phodopus*, *Megacricetodon* ($m2/m1 = 0.72$ to 0.99 and $m3/m1 = 0.44$ to 0.82: $m1 > m2 > m3$). Within the arvicoline group, a smaller difference can be noticed between *Promimomys* and the other arvicolines, that is, between $m1 > m2 = m3$ and $m1 \gg m2 = m3$. In addition, *Prometheomys* can be considered far outside the other group of arvicolines (Fig. 3).

A NEW MODEL FOR THE ARVICOLINAE

With the IC model, we were not able to predict the peculiar vole molar proportions. To determine the best mathematical model available to reflect vole lower molar proportions, several simple linear regressions were tested: least-square adjustment, major axis, and reduced major axis, but all of them are unsatisfactory in term of regression coefficient ($R^2 = 0.56$ in least-square regression and the explained variance by the major axis and reduced major axis is about 0.50). In addition, the requirement of normality for these regressions is not met by the molar ratio data. For these reasons, it was necessary to find another model which best fits the relationship between the three molars: the multiple regressions.

In the multiple regressions of three variables ($m1$, $m2$, and $m3$), the best relationship (minimizing the vertical least squares) for fitting the three-dimensional point cloud data is checked. It amounts to determining the b_0, b_1, and b_2 coefficients such as:

$$m3 = b_0 + b_1 m1 + b_2 m2 + \varepsilon$$

where ε = residual.

This method enables the calculation of the significant coefficients and gives the proportion R^2 of variance explained by the model. To highlight the dynamic relationships between the molar areas, we start with the explanation of the variable $m3$ as a function of $m1$ and $m2$ (multiple regressions), then, $m2$ as a function of $m1$ and, $m3$ as a function of $m2$ (simple regressions). This approach is justified by the high values of simple correlations between the three molar areas (see R^2 values in Table 2).

To validate this model we applied it to the murine molar areas available in the Kavanagh et al. datasets. The multiple and simple regression results obtained for murines are presented in Table 2A. We will now look in detail at these results. For each regression presented below, only those coefficients significantly different from zero will be included in the formulas.

Contrary to voles, the multiple regressions on murines show that the $m3$ size is simply predicted by the $m1$ size:

$$m3 = 0.66\, m1$$

Table 2. Results on multiple and simple regressions on murine data (A), from Kavanagh et al. (2007), arvicoline data (B), without outliers, vole data (C), lemming data (D), and cricetine data (E). Bold characters correspond to significant probabilities (*P* level) for the b coefficients affected to the variables. Orig. Ord., Origin ordinate.

A	Murines n=29	b coefficients	P level	C.I. min (95%)	C.I. max (95%)	R^2
	$m3$ versus $m1m2$					
	Orig. Ord.	−0.940	0.154	−2.257	0.376	*0.837*
	m1	**0.655**	**0.000**	**0.381**	**0.928**	
	$m2$	0.068	0.678	−0.263	0.399	
	$m2$ versus $m1$					*0.789*
	Orig.Ord.	0.047	0.951	−1.522	1.617	
	m1	**0.733**	**0.000**	**0.583**	**0.883**	
	$m3$ versus $m2$					*0.684*
	Orig. Ord.	0.008	0.993	−1.702	1.717	
	m2	**0.772**	**0.000**	**0.565**	**0.979**	

B	Arvicolines n=225	b coefficients	P level	C.I. min (95%)	C.I. max (95%)	R^2
	$m3$ versus $m1m2$					*0.957*
	Orig. Ord.	0.027	0.330	−0.027	0.081	
	m1	**−0.275**	**0.000**	**−0.343**	**−0.207**	
	m2	**1.298**	**0.000**	**1.192**	**1.405**	
	$m2$ versus $m1$					*0.945*
	Orig. Ord.	**−0.134**	**0.000**	**−0.199**	**−0.070**	
	m1	**0.619**	**0.000**	**0.600**	**0.638**	
	$m3$ versus $m2$					*0.944*
	Orig. Ord.	**−0.073**	**0.008**	**−0.128**	**−0.019**	
	m2	**0.878**	**0.000**	**0.850**	**0.907**	

C	Voles n=213	b coefficients	P level	C.I. min (95%)	C.I. max (95%)	R^2
	$m3$ versus $m1m2$					*0.973*
	Orig. Ord.	−0.005	0.811	−0.042	0.033	
	$m1$	0.004	0.907	−0.060	0.068	
	m2	**0.807**	**0.000**	**0.701**	**0.913**	
	$m2$ *versus* $m1$					*0.970*
	Orig. Ord.	**−0.098**	**0.000**	**−0.144**	**−0.052**	
	m1	**0.594**	**0.000**	**0.579**	**0.608**	
	$m3$ versus $m2$					*0.973*
	Orig. Ord.	−0.004	0.833	−0.038	0.030	
	m2	**0.813**	**0.000**	**0.795**	**0.832**	

D	Lemmings n=12	b coefficients	P level	C.I. min (95%)	C.I. max (95%)	R^2
	$m3$ versus $m1m2$					*0.611*
	Orig. Ord.	0.364	0.673	−1.524	2.252	
	$m1$	0.368	0.488	−0.774	1.510	
	$m2$	0.426	0.501	−0.949	1.800	
	$m2$ versus $m1$					*0.86*
	Orig. Ord.	−0.148	0.738	−1.111	0.813	
	m1	**0.771**	**0.000**	**0.552**	**0.989**	
	$m3$ versus $m2$					*0.588*
	Orig. Ord.	0.649	0.389	−0.956	2.253	
	m2	**0.837**	**0.004**	**0.343**	**1.330**	

Continued.

Table 2. Continued.

E	Cricetines n=34	b coefficients	P level	C.I. min (95%)	C.I. max (95%)	R^2
	$m3$ versus $m1m2$					*0.962*
	Orig. Ord.	−0.043	0.552	−0.187	0.102	
	$m1$	−0.192	0.276	−0.544	0.161	
	m2	**1.089**	**0.000**	**0.780**	**1.398**	
	$m2$ versus $m1$					*0.954*
	Orig. Ord.	−0.066	0.420	−0.230	0.098	
	m1	**1.115**	**0.000**	**1.028**	**1.202**	
	$m3$ versus $m2$					*0.960*
	Orig. Ord.	−0.068	0.322	−0.205	0.069	
	m2	**0.925**	**0.000**	**0.858**	**0.991**	

Simple regressions indicate that $m2$ size is strongly influenced by $m1$ size ($m2 = 0.73\ m1$) and that $m3$ size is equally influenced by $m2$ size ($m3 = 0.77\ m2$). As the Kavanagh et al. model suggests, the $m1$ inhibits both the $m2$ and the $m3$.

Table 2B shows the multiple regression results obtained from the global sample of arvicolines. The obtained residuals follow a normal distribution. When the value of residuals for an individual was very high, it was considered that it was not well represented by the model and was analyzed separately. Most of the individuals with high residual values correspond to lemmings, but also included *Prometheomys* and *Allophaiomys* (see Supporting Information). For the global sample of arvicolines, the multiple regressions between $m3$ versus $m2$ and $m1$ (Table 2B) give a model in which an influence of both $m1$ and $m2$ is registered on the $m3$ by the equation:

$$m3 = -0.28\ m1 + 1.30\ m2$$

It can be noticed that the $m1$ influence on $m3$ is assigned with a negative coefficient. The $m2$ size has a positive influence on the $m3$: as the $m2$ get larger, the $m3$ get 1.3-fold larger. Simple regression between $m2$ and $m1$ (Table 2B) gives a model in which

$$m2 = -0.13 + 0.62\ m1$$

The $m2$ size is much smaller than the $m1$ size. The $m1$ has a positive influence on $m2$. These two molars evolve in parallel with a proportional coefficient of 62%. Simple regression between $m3$ and $m2$ (Table 2B) indicates that

$$m3 = -0.07 + 0.88\ m2.$$

The sizes of $m2$ and $m3$ are quite similar but $m3$ is consistently smaller.

Detailed analysis of the residuals shows that most of the lemmings (50%) are not well represented by this mathematical model (the R^2 coefficient is closer to 1 without these individuals). It is then justified to consider voles and lemmings separately within the model. For voles only (Table 2C) the same multiple and simple regressions were done on the 213 remaining individuals. The results summarized in the Table 2C show that, for the multiple regressions, the $m1$ does not influence significantly the $m3$ size prediction as the equation gives:

$$m3 = 0.81\ m2$$

However, the relationship between $m1$ and $m2$ areas is close to the model defined in the global sample as:

$$m2 = -0.10 + 0.59\ m1$$

In voles, the relationships between the three molars indicate that $m1$ has no influence on $m3$ but has a great influence on $m2$. Only the $m2$ can predict the $m3$ size. Therefore, there is mediation between the three molars. The $m2$ can be seen as the mediator variable between $m1$ and $m3$.

For the lemming data (Table 2D), the multiple regression model is unsatisfactory for two reasons: (1) none of the b coefficients of the model are significant and (2) the R^2 coefficient is not as high as for voles. There is probably a sample bias as only 12 individuals are taken into account. Nevertheless, in simple regression, the $m1$ and $m2$ sizes relationship is relevant ($R^2 = 0.86$) as

$$m2 = 0.77\ m1$$

A fundamental difference is underlined here between the vole and lemming area relationships of $m1$ and $m2$. The influence of $m1$ is higher in the lemming group than the vole group. However, the $m2$ influence on the $m3$ is similar in the two groups.

Furthermore, we tested this multiple regression model on the cricetine molar areas, as they represent an ancestral molar pattern for arvicolines and murines. We obtained another model closer to the vole model. Indeed, Table 2E shows a multiple regression

model in which only the $m2$ size predicts the $m3$ size and $m2$ size is equal to $m3$ size:

$$m3 = 1.09\ m2$$

For the linear regressions, the influence between $m1$ and $m2$ ($m2 = 1.12\ m1$) is equivalent to the influence of $m2$ on $m3$ ($m3 = 0.93\ m2$).

Discussion

ARVICOLINAE DEVELOPMENTAL NOVELTY

Our results reinforce the peculiarity of voles and lemmings and develop the possibility that the linear IC model may not be applied across all mammals. We highlight a phenotypic tendency in arvicolines from $m1 \gg m2 = m3$ to $m1 > m2 = m3$. This phenomenon could be explained by a varying inhibition for $m1$ throughout development of the lower dental row (Figs. 1, 2) or by a discontinuation of the influence of $m1$ on the remainder of the tooth row after some point in time. Therefore, we have demonstrated that this model, established from murine measurements, does not predict adequately molar proportions in arvicolines. In fact, a multiple regression model is more appropriate to reflect the arvicoline molar relationships. Our measurements show that all arvicolines have a large $m1$ compared to the other molars and that their $m2$ size is almost always equal to the $m3$ size. This singularity of arvicoline $m1$ has already been underlined by Jernvall et al. (2000a) and Salazar-Ciudad and Jernvall (2002) who suggest that arvicoline $m1$ development is different from murine $m1$, but also from other mammals (Kavanagh et al. 2007). Three hypotheses can be formulated.

First, Kavanagh et al. (2007) hypothesized that the greatly elongated anterior part of the arvicoline $m1$, observed by Jernvall et al. (2000a) and Guthrie (1965), is allowed during development by the absence of premolars in the anterior part of the lower dental diastema. In addition, rodents with large lower fourth premolar ($p4$) erupted (e.g., glirids, sciurids) do not have an elongated $m1$ in the anterior part compared to the $m2$ and $m3$ (Hillson 2005). Furthermore, Viriot et al. (2002) has demonstrated in murine lower jaws that, historically, the loss of premolars through time may have favored the formation of more anteroconid cusps. Then, it would be advocated that the ultimate reason for why the $m1$ "could" elongate is the lack of premolars.

Second, it was demonstrated that the longitudinal growth of $m1$ is faster in voles than in mice (Jernvall et al. 2000a). So, at the same embryonic time (embryonic day 15), the acceleration of the longitudinal development of the first lower molar in voles can explain their greatly elongated anterior part. Furthermore, diagonal spatial shifting of cusps in voles is explained by a model in which: (1) longitudinal growth is higher, and (2) more inhibition of activators by inhibitors is involved in $m1$ development (Salazar-Ciudad and Jernvall 2002), that is, the *a*/*i* ratio decreases, in the IC model. As a result, the hypothesis of faster growth for arvicoline $m1$, in relation to murine $m1$, is congruent with experimental and model results, to explain partly the elongated $m1$ in arvicolines.

Third, it can be hypothesized that, compared to mice, the larger anterior part of the lower $m1$ in voles can result from the incorporation of more proximal diastemal (premolar) buds into the $m1$ in voles than in mice. Peterková et al. (2006) suggested that arvicolines incorporate two vestigial buds in their lower $m1$ anterior part, whereas only one is incorporated in the mouse. This hypothesis in the mandible can be supported by results obtained in molar development in the maxilla. During development, differences between the vole and mouse are noted in the number of incorporated premolar buds into the $m1$ anterior part. One bud is incorporated in the vole $m1$ at the end of the bud stage (embryonic day 14), whereas no buds are incorporated in the mouse (Witter et al. 2005). However, the incorporation of one vestigial premolar does not involve an elongation of the anterior part, neither for the upper $m1$ of voles, nor for the lower $m1$ of mice. In voles, the elongation is usually situated in the posterior part of the third upper molar (Guthrie 1965). It is then difficult to advocate a great elongation of the lower $m1$ anterior part with the incorporation of vestigial premolars, even with two vestigial buds, without strong developmental observations on vole teeth to confirm it.

Consequently, the highly elongated first lower molar of arvicolines might rather be explained by a faster growth of the anterior part (ED = 15), which may be favored by the premolar disappearance in the diastema (ED = 14). In addition, the fast growth of the $m1$ anterior part may be related to a strong decrease of the *a*/*i* ratio within the molar.

ARVICOLINAE DEVELOPMENTAL SCENARIOS

The multiple regression model does not demonstrate the mechanisms involved in the varying molar proportions, but instead it describes the best relationships that exists between the molars. We demonstrate in arvicolines that $m1$ influences the $m2$ size ($m1 \gg m2$) and that both $m1$ and $m2$ can predict the $m3$ size. However, for voles, only the $m2$ area predicts the $m3$ size and the $m1$ does not predict the $m3$ size. Therefore, it is possible that $m2$ mediates the effect of $m1$ on $m3$. Afterwards, we might hypothesize that the inhibition of $m1$ on $m2$ may increase and the inhibition of $m2$ on $m3$ may decrease. We have already seen that a part of the greatly elongated $m1$ of voles may be explained by an increasing inhibition of activators by inhibitors, that is, a decrease in the *a*/*i* ratio. Yet, in the IC model, a decrease in the *a*/*i* ratio leads to smaller posterior molar. Then, the elongated $m1$ development may involve decreasing posterior molar size.

As the arvicoline regression line is parallel to the arvicoline ICR regression line, then the arvicoline molar proportions seem

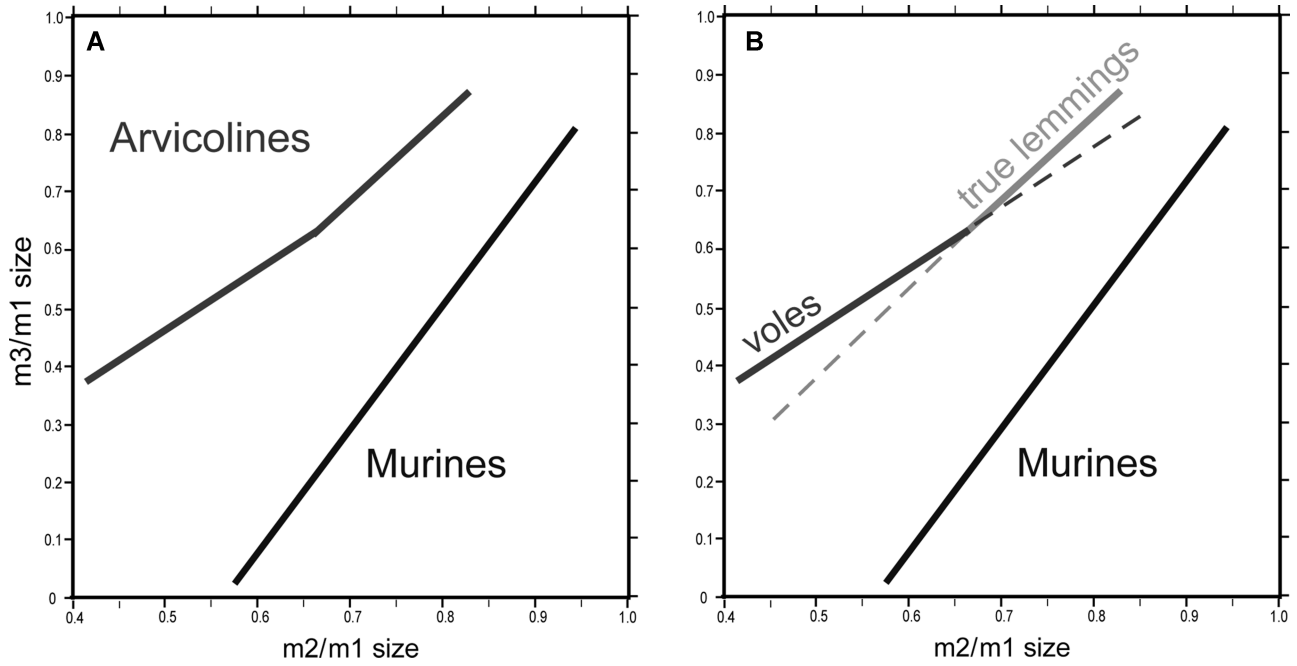

Figure 5. Summary of the two patterns in arvicoline molar proportions. (A) Nonlinear molar proportions: a breakdown is observed within the extant arvicoline regression. The inhibition changes between $m1 \gg m2 = m3$ and $m1 > m2 = m3$. (B) Two different linear models between voles and true lemmings. There are two linear regressions for voles ($y = 1.120x - 0.174$; dark gray line) and true lemmings ($y = 1.887x - 0.623$; light gray line). No break is observed in the murine regression (black line) illustrating the linear IC model in both diagrams (Kavanagh et al. 2007).

to act in a "random-like" linear manner, or at least there is a degree of independence of the *m*3 from the *m*1. However, within the arvicolines, it is possible to distinguish two groups formed by different molar proportions: voles and true lemmings (Figs. 2, 5). Therefore, one of two cases could be advocated: either a two-part linear regression for the arvicolines (Fig. 5A), or two different linear models for voles and lemmings separately (Fig. 5B). In the first case, a single nonlinear model may characterize the linear breakdown. In the second case, two linear models, responding to the IC model or not, may be differentiated within the arvicolines.

The multiple regression model reflects strong differences between the vole and lemming molar relationships. Lemming molar area relationships seem to more closely reflect the linear IC model. However, a large enough sample size is not available to confirm it. As a result, two different linear models may explain the voles and lemmings molar proportions (Fig. 5B).

The most recent published phylogenies of arvicolines (Galewski et al. 2006; Robovsky et al. 2008; Buzan et al. 2008) recognize the different tribes (Arvicolini, Lemmini, Dicrostonyichi . . .) and clearly differentiate all the lemmings (Lemmini and Dicrostonyichi) from Arvicolini. Nevertheless, in our results, molar proportions of the tribe Dicrostonyichi fall into the Arvicolini distribution (Fig. 3). Only the true lemmings (Lemmini) express different molar proportions. This would confirm the differences expressed between voles and true lemmings.

One other genus, *Prometheomys*, has a peculiar molar proportion compared to all the other arvicolines and close to murines. Several authors (Kretzoi 1969; McKenna and Bell 1997; Musser and Carleton 2005; Galewski et al. 2006) suggest that this genus could represent an archaic line and thus be isolated as a tribe Prometheomyini. Furthermore, this genus emerges first within the arvicoline phylogeny based on mitochondrial and nuclear DNA (Galewski et al. 2006).

We can see two main ways in which the molar proportions along the tooth row can be altered and therefore that arvicolines can depart from the expected pattern: (1) change the influence of an early tooth (e.g., *m*1) on the development of a later tooth (e.g., *m*2) so that the inhibition of later teeth no longer follows the specific murine inhibitory cascade rule ($Y = 1 + [(a - i) / i] [X - 1]$); (2) the addition of prisms to the *m*1, with a consequent increase in size, that does not influence the inhibitory cascade along the tooth row. In the first case, there may be no pattern at all to the relative tooth sizes along the tooth row (i.e., a random occupation of dental proportion morphospace), or a different pattern from that found in murines may exist (e.g., a different line or perhaps a region in morphospace). In the second case, the molars do follow the inhibitory cascade rule, with the exception that the *m*1 is larger than expected.

To determine whether the second method is a likely cause of the difference in arvicoline molar proportions, we artificially

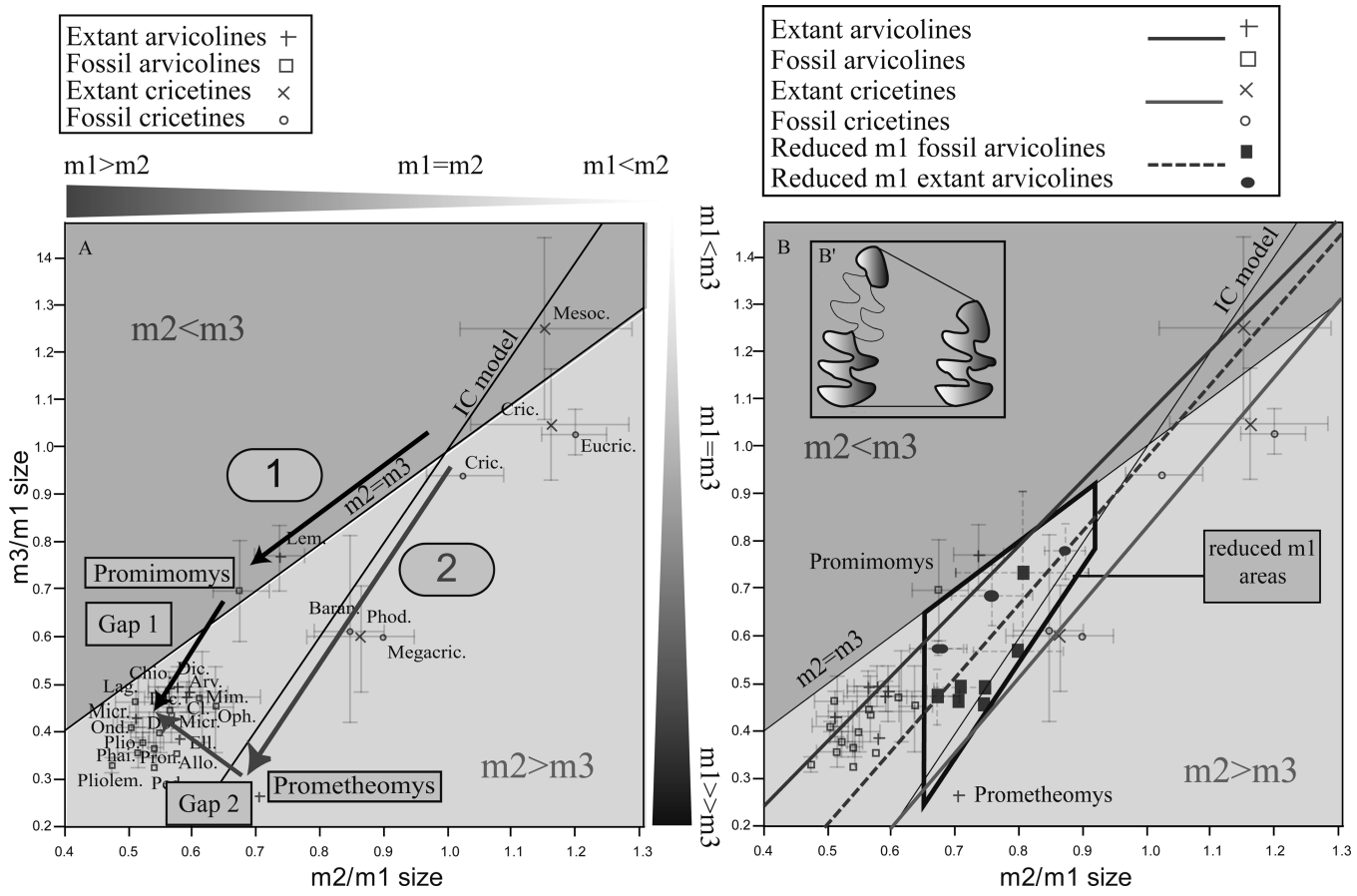

Figure 6. Hypotheses of the arvicolinae evolution from cricetinae. (A) Two scenarios may be involved in the arvicoline molar proportion evolution from cricetines. Black arrows represent the evolutionary trajectory from cricetines to the oldest arvicoline genus *Promimomys* and from *Promimomys* to the more recent genera (1). Gray arrows describe the second scenario in which *Prometheomys* molar proportions derived from cricetines and then lead to all other arvicolines (2). (B) New molar proportions with reduced *m*1 area (three prisms left, see the B′ box) are encapsulated inside the area surrounded by a black thick line.

reduced the *m*1 size of 19 extant and fossil arvicolines (see Supporting Information) to transform them into the nonderived molar pattern. We kept only the three first prisms of the *m*1 posterior part (*Promimomys* and *Prometheomys* forms) and the anterior loop. This therefore shows the relative proportions of the molars without the additional prisms. It can be observed that the molar proportions of arvicolines obviously change and are higher than the real molar proportions (Fig. 6B).

However, the reduced lower molar proportions of arvicolines still do not follow the linear IC model, but they are closer than the unaltered proportions. The arvicoline line is rather close to the cricetine and *Promimomys* molar sizes (Fig. 6B, Table 1).

ARVICOLINAE EVOLUTION

The addition of fossil data (arvicolines and cricetines) allows us to project a time scale onto the developmental model obtained in extant arvicolines to describe an evolutionary trend. We demonstrate, from extant and fossil arvicoline lower molar proportions, that throughout arvicoline evolution, there might be two large gaps in molar proportions: (1) from the oldest arvicoline genus *Promimomys* to all other more recent genera, except for *Lemmus*; or (2) from *Prometheomys* to all other arvicolines (Fig. 6A). These phenotypic trajectories are strengthened by the cricetine position in the morphospace in which $m1 = m2 = m3$. Indeed, the most reliable molecular phylogenies (Steppan et al. 2004; Galewski et al. 2006), established on nuclear and mitochondrial genes, support the cricetine basal position for arvicoline in muroid reconstructions. Therefore, two trajectories of arvicolines from cricetines may be involved (Fig. 6A) corresponding to the gaps observed in molar proportions: (1) the main group of voles derived from the oldest fossil *Promimomys* or (2) they derived from the most "primitive" modern genus *Prometheomys* (Galewski et al. 2006). However, only two individuals represent the genus *Promimomys* and one individual characterizes the genus *Prometheomys*.

McKenna and Bell (1997) reported the first appearance of the *Prometheomys* genus in the Asian fossil record dated from the Late Pleistocene (≈130 ka). If *Prometheomys* led to the more recent arvicolines, this genus should be older than the oldest

arvicoline genus in the major group, *Mimomys*. However, the genus *Mimomys* (which appeared in Europe at about 3.6 Ma; Chaline 1987; McKenna and Bell 1997; Chaline et al. 1999; Kowalski 2001) is much older than *Prometheomys*. Therefore, this temporal inadequacy reinforces the *Promimomys* origin of the more recent molar proportions in arvicolines. As a result, we confirm that the arvicoline evolutionary trajectory derived from a slight change of $m1$ size between cricetines ($m1 = m2 = m3$) and *Promimomys* ($m1 > m2 = m3$). Then, the rapid acquisition of a large $m1$ in arvicolines (leading to $m1 \gg m2 = m3$) could explain the gap observed in molar proportions from *Promimomys* rather than from *Prometheomys*.

Consequently, we could deduce that there might not have been a gradual evolution in molar proportions in contrast to the gradual morphological evolution hypothesized by some authors from observations on the occlusal surface evolution (Chaline and Sevilla 1990; Chaline and Brunet-Lecomte 1992; Néraudeau et al. 1995). Instead, this may represent a scenario of punctuated evolution in which this leap in molar proportions in the first stages of arvicoline evolution (between 3.8 and 2 Ma) could be congruent with the radiation event ($\approx$ 2 Ma ago) registered in the arvicoline fossil record (Chaline et al. 1999) and with molecular clock ages (between 4.4 and 2.6 Ma, Conroy and Cook 1999). This hypothesis is also congruent with a nonlinear development allowing run-away changes in molar size. In fact, the major changes in molar relationships between voles and cricetines are the unequal distribution of the inhibition through the three molars. Cricetines have molar relationships in which $m1 = m2 = m3$, which might be shifted in arvicolines $m1 \gg m2 = m3$ and murines $m1 > m2 > m3$ through time. Therefore, the rapid acquisition of a large $m1$ in arvicolines could be seen as an advantage and a response to selection as it has also been mentioned by Kavanagh et al. (2007). Indeed, not just molar proportions but also tooth pattern began to be highly specialized (prismatic pattern and increasing high-crown molars) as food became very abrasive. In comparison with the pattern found in other groups of rodents during quaternary time (i.e., bunodont form), the prismatic pattern of vole molars could provide a better adaptation to the abrasive vegetation found in steppes and meadows in which voles and lemmings usually live (Nadachowski 1984; Marchand et al. 2003; Montuire and Brunet-Lecomte 2004; Nappi et al. 2006).

Nevertheless, essentially three features can be distinguished on the structure of tooth row: (1) molar proportions, (2) occlusal tooth design and enamel structure (e.g., bunodont, lophodont, prismatic: see von Koenisgwald 1980, 1982; Janis 1995, 2000; Evans et al. 2005, 2007; Lucas et al. 2008), and (3) crown growth (hypsodonty versus brachyodonty; see Jernvall et al. 2000b; Jernvall and Fortelius 2002; Fortelius et al. 2003; MacFadden 2005). However the occlusal tooth complexity is probably the most linked to diet (Evans et al. 2007) and thus to vegetation.

In conclusion, we suggest that the elongated anterior part of vole $m1$ is explained by faster longitudinal growth probably favored by the absence of premolars. Faster longitudinal growth of the first molar may induce for voles, an increasing inhibition of posterior molar development in voles, or in fact be independent of the inhibition of posterior molars, which remain approximately the same size. We explain that the need for a multiple regression model to characterize the vole distinctiveness ($m1 \gg m2 = m3$, Fig. 1) implies that the linear IC model is not sufficient in explaining, or predicting, vole molar evolution. In addition, we demonstrate from fossil molar area measurements (Figs. 2, 3) that the evolution of arvicoline molar proportions might be characterized by a gap corresponding to the rapid acquisition of a large $m1$ contemporaneous to arvicoline radiation. This acquisition can be viewed as an adaptive advantage for consuming abrasive food. Therefore, questions still remain in rodent evolution to explain the two different trajectories of development taken by arvicolines and murines. It can be suggested that a shift in the distribution of inhibition between the three molar happened from the cricetine molar pattern.

Our approach not only provides new insights on the IC model of Kavanagh et al. (2007) but also describes a new model that can characterize nonlinear molar proportions in mammals. It also underlines the essential focus on fossil data in evolutionary developmental studies to highlight macroevolutionary trajectories through time.

ACKNOWLEDGMENTS

We thank for helpful discussions H. Lesot and G. Escarguel, for help with scientific revisions; E. Escudé and C. Tougard, for tooth supply from CBGP collections of Montpellier and MNHN collections of Paris; J.-P. Quéré and C. Denys, respectively; and for English revisions, C. Chateau-Smith. This work was supported by Biogéosciences laboratory (University of Burgundy, France) and by a doctoral Fellowship (Grant MENRT, Ministère de l'Enseignement Supérieur et de la Recherche, France).

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Associate Editor: B. Swalla

Supporting Information

The following supporting information is available for this article:

Table S1. Measurements of arvicoline and cricetine molar areas. CBGP, Biology Center of Population Control (International Campus of Baillarguet, France); UBGD, University of Burgundy Geology Dijon (Dijon, France).

Table S2. Measurements of arvicolines with reduced first lower molar (*m*1) areas. *m*2 and *m*3 areas are still unchanged.

Supporting Information may be found in the online version of this article.
(This link will take you to the article abstract).