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Craniofacial Growth in Apert Syndrome as Measured by Finite-Element Scaling Analysis

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Abstract. A new tool for the study of biological form change is applied in a comparison of craniofacial growth in normal children and those affected with Apert syndrome. Using finite-element scaling analysis, the magnitude of size change during postnatal growth in the Apert sample was determined to be generally less than normal, and the magnitude of shape change was generally greater than normal. No consistent, statistically significant, alteration from normal growth was defined in the Apert sample, however. There appears to be no consistent effect on general cell and tissue proliferation in Apert syndrome. Rather, specific subpopulations of cells and tissues may be affected differentially over time.

Introduction

In 1917, D'Arcy Thompson wrote:

'... the form of an object is defined when we know its magnitude, actual or relative, in various directions; and Growth involves the same concepts of magnitude and direction, related to the further concept or "dimension" of Time' [Thompson, 1917].

In keeping with Thompson's definition, this study uses finite-element scaling (FES) analysis to quantify growth as the difference between forms in terms of *magnitude* of change in specified *directions.*

Measuring Form Change Using FES

FES and closely related methods, e.g. biorthogonal grids [Bookstein, 1978, 1983, 1984], are currently being applied with success to the study of biological form change [Skalak et al., 1982; Cheverud et al., 1983; Grayson et al., 1985; Lavelle, 1985; Cheverud and Richtsmeier, 1986; Lozanoff and Diewart, 1986; Richtsmeier and Cheverud, 1986; Moss et al., 1987; Richtsmeier, 1987]. The FES methods used in this study were developed by Lewis et al. [1980], and are based on principles from finite-element analysis and continuum mechanics. Several explanations of the method as applied to biological forms are available from the literature cited above. Here, I will simply highlight the features crucial to an elementary appreciation of the method.

First, FES analysis is a method of comparisons requiring a minimum of two objects for analysis. The method is registration-free, cancelling the need for orienting subjects for comparison. The coordinates of anatomical landmarks serve as raw data and are used to divide the biological forms into sections called 'finite elements'. Finite elements

are simply constructs used to model the forms under study. The boundaries of finite elements are defined by lines which connect landmarks at the vertices of the elements. Changes in form occur by expansion and/or contraction of material in the area surrounding the landmarks, causing the landmarks to appear to move in relation to one another. The landmarks, however, are stable; they do not move.

It is convenient to think of the information produced by these comparisons called *deformations* as instructions for producing the second form from the initial form by altering the morphology surounding given landmarks. In this analysis, the morphological change is considered representative of growth. Three simple measures (scalars) of local form change are determined from the information provided by a form change tensor. The measures used here to quantify the difference between forms are: size change magnitude, shape change magnitude and directions of shape change.

FES determines the principal directions of morphological difference between two forms local to each landmark. The values associated with each principal direction represent the magnitude of change along that axis. Two principal directions specify the geometric orientation of the greatest and least shape differences between the forms local to each landmark with reference to the coordinate system of the reference form.

Figure 1 is a schematic representation of the segregation of form change into two independent components, size and shape. P1 and P2 are the magnitudes of change along the two principal directions of form change. Size change is expressed as the average magnitude of change along the principal directions, or the uniform aspect of form change, and can be conceptualized geometrically as the degree to which a circle centered on a landmark expands or contracts [size $\Delta = t = (P1 + P2)/2$]. Shape change is the nonuniform aspect of form change, expressing the difference or variation of change along the principal directions, or the degree to which the circle is deformed into an ellipse [shape $\Delta = s = abs(P1-P2)/2$]. The area of the shape change ellipse equals the area of the reference circle, thereby excluding all size change from this measure. Size and shape change magnitudes are expressed on the same scale and can therefore be compared between landmarks within a deformation as well as across deformations.

FES measures size and shape differences between forms local to all landmarks. A mean of these measures of local size change, called total size ($\bar{s}$), represents the average magnitude of size change across the entire form. Total

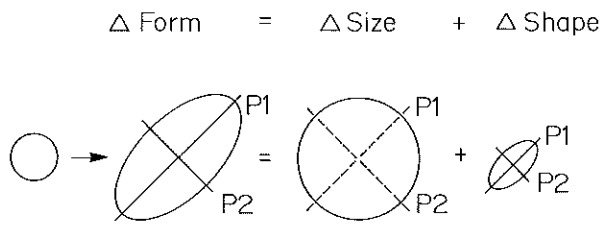

Fig. 1. Graphic representation of the division of form change into size change and shape change. The circle to the left of the arrow represents the reference form, and the ellipse to the right of the arrow represents the target form. The principal directions of form change and the associated magnitudes, P1 and P2, are diagrammed. They are dashed for size change because their placement is arbitrary: the change is equal in all directions. The maximum and minimum magnitudes of shape change occur along the axes defined by the principal directions.

shape ($\bar{t}$) is the average magnitude of shape change across the entire form, but does not incorporate information concerning the direction of these changes. An alternate summary measure of shape change, global shape change (tg) [see Cheverud and Richtsmeier, 1986], describes spatial variation in local *size* change magnitudes and is calculated as the standard deviation of local size changes within a biological form.

FES analysis identifies the principal directions of form difference local to each landmark with reference to the coordinate system of the reference object. Although the choice of the coordinate system is arbitrary and the directions of form change are in no way dependent upon this system, when comparing directions specified by deformation analyses that utilize different reference forms, principal directions are rotated to a common coordinate system [details of a simple rotation are found in Richtsmeier, 1985, 1987]. Since principal directions are orthogonal, only one of the transformed directions is needed to determine the similarity of directions of form change defined for several comparisons.

FES Analysis of Growth in Apert Syndrome

Materials and Methods

Two samples of serial cephalometric radiographs are used in analysis. The normal sample comes from the Bolton-Brush Growth Study Center [Broadbent et al., 1975], Case Western Reserve University, Cleveland, Ohio. The sample of Apert cases comes from the Center for Craniofacial Anomalies, University of Illinois, Chicago, Ill. Apert syndrome is characterized by premature closure of cranial sutures and syndactyly of the hands and feet. Individuals diagnosed with Apert syndrome are usually characterized by hypertelorism, exophthalmos, maxillary hypoplasia

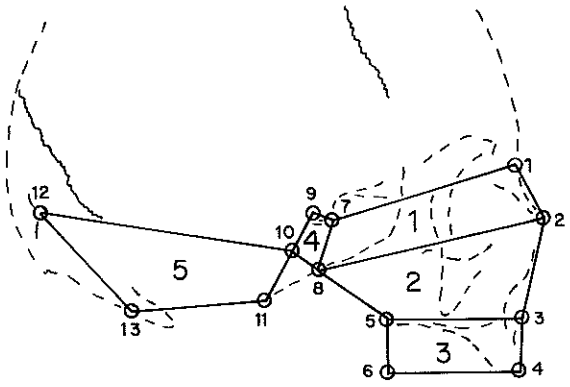

Fig. 2. Two-dimensional projection of human craniofacial complex divided into 5 elements used in FES analysis. Definition and boundary trace of the elements are as follows: element 1, upper face = nodes 1, 7, 8, 2; element 2, middle face, nasomaxillary area = nodes 2, 8, 5, 3; element 3, lower face, palate = nodes 3, 5, 6, 4; element 4, superior portion of posterior cranial base or basisphenoid = nodes 7, 9, 10, 8; element 5, occiput = nodes 10, 12, 13, 11. Refer to table I for definition of landmarks.

and mandibular prognathism. The disorder has been described as having an age-dependent component [Kreiborg and Pruzansky, 1981]. All Apert cases used in this analysis are considered as classical forms of Apert syndrome by Kreiborg and Pruzansky [1981]. None of the cases considered had undergone any major surgical procedures, but a few of the Apert individuals had experienced early suture release. Detailed descriptions of the data, data collection procedures, methods for correction of enlargement, and preparation of the two-dimensional data for FES analysis are given by Richtsmeier [1985]. Two-dimensional coordinates of 13 landmarks plotted on the tracings of each individual were used as raw data and are defined in table I.

Four constructed landmarks are used (table I). These landmarks are not true biological loci, but are located geometrically using information from 2 other landmarks and a single anatomical structure. The locations of the constructed points are not analogous to 'extremal' points [Moyers and Bookstein, 1979], and are not dependent upon any particular coordinate system. However, the size and shape magnitudes calculated for these points probably reflect form change local to the landmarks used to construct them to a certain degree.

The age intervals used in this growth study were chosen on the basis of availability of longitudinal records of Apert cases. The specific Apert and normal cases used are not constant across age intervals. Sample sizes (normal, Apert) for each age interval are: 1–4 years (10, 4); 4–6 years (10, 3); 10–13 years (10, 4); 14–17 years (10, 4).

The lateral projection of the human craniofacial complex was divided into 5 elements which are diagrammed and defined in figure 2. In each of the four age intervals considered, the finite-element model of the younger of the paired films was used as the reference form and mapped into the homologous elements of the older film. Each mapping quantifies local principal directions and magnitudes of form change occurring due to growth of an individual during the specified age interval. Individual measures of local size change (s) and local shape change (t) occurring due to growth were calculated from the principal values. Statistical analyses were conducted to determine intersample differences.

Table I. Definition and description of landmarks used in analysis

Landmark No. and abbreviation	Point location and description
1–NAS:	nasion
2–NSL:	nasale
3–ANS:	anterior nasal spine
4–IDS:	intradentale superior. Located on the alveolar border of the maxilla between the central incisors
5–PNS:	posterior nasal spine
6–PCP:	palatal constructed point. Constructed by drawing a line in an inferior direction from point 5 and a line in a posterior direction from point 4 (parallel to the line stretching from nodal point 3 to nodal point 5). These lines are drawn to meet at a 90° angle at point 6
7–SEF:	sella floor. Most concave point of sella turcica. Sella turcica is defined as that area along the hypophyseal fossa bounded by tuberculum sella and posterior sella
8–SBAF:	constructed point of sphenoid body, anterior face. Points 8 and 10 are constructed by drawing a line to connect sella floor and basion. At the midpoint of this line, a perpendicular is drawn. This constructed line approximates the spheno-occipital synchondrosis. The point at which this line intersects with the anterior surface of the body of the sphenoid and/or basal portion of the occipital bone is defined as point 8. The point at which this line intersects the intracranial or neural surface of the sphenoid body and/or basal portion of the occipital bone is defined as point 10
9–PSL:	posterior sella
10–SBNS:	constructed point of sphenoid body, neural surface (see description of point 8)
11–BAS:	basion
12–CRU:	internal occipital proteburance of cruciate eminence
13–CPNC:	constructed point on neurocranium. Point 15 is constructed by drawing a line that connects points 11 and 12. This line is then bisected by a perpendicular. The point at which this line intersects the exterior surface of the squamous portion of the occipital bone is point 13

Results

Size Change. The average local size change values, the results of F tests for differences in sample variances and those of t tests for differences in sample means are presented in table II. In general, growth in size as quantified by FES analysis does not appear to be more variable among Apert individuals than among normal individuals.

Table II. Means of individual local size change magnitudes (s) between reference (younger) form and target (older) form for Apert and normal samples; also included are total size change magnitudes ($\bar{s}$) and global shape magnitude (tg)

Landmark	Age interval, years			
	1–4	4–6	10–13	14–17
Apert				
NAS	0.110	0.078	0.024	0.002
NSL	0.127	0.053	0.037*	0.018
ANS	0.152	0.051[A]	0.070	0.018**
IDS	0.168	0.023[A]	0.074	0.040
PNS	0.190	0.068	0.064	0.040
PCP	0.191	0.024[A]	0.072	0.024
SEF	0.071[A]	0.040	0.043	0.039
SBAF	0.085*	0.035	0.053	0.058
PSL	0.102	0.040	0.042	0.035
SBNS	0.066	0.030	0.060	0.040
BAS	0.071	0.021	0.059	–0.003
CRU	0.051**	0.038	–0.031*	–0.010
CPNC	0.047**	0.043	–0.040**	–0.023
$\bar{s}$	0.110	0.042	0.041	0.021
tg	0.051	0.017	0.037	0.024
Normal				
NAS	0.117	0.051	0.058	0.013
NSL	0.141	0.062	0.069	0.050
ANS	0.194	0.057	0.061	0.057
IDS	0.194	0.050	0.060	0.039
PNS	0.262	0.064	0.066	0.032
PCP	0.199	0.056	0.053	0.036
SEF	0.125	0.040	0.045	0.066
SBAF	0.158	0.056	0.058	0.058
PSL	0.133	0.019	0.049	0.053
SBNS	0.110	0.035	0.036	0.033
BAS	0.098	0.037	0.028	0.011
CRU	0.105	0.022	0.015	–0.003
CPNC	0.119	0.015	0.004	–0.018
$\bar{s}$	0.150	0.043	0.046	0.033
tg	0.049	0.017	0.020	0.026

See table I for abbreviations of landmarks. *p = 0.05; **p = 0.10: intersample mean difference significant.

[A] Intersample variance difference significant (p = 0.05): variance is larger in the Apert sample.

Table III. Means of individual local shape change magnitudes (t) between reference (younger) form and target (older) form for Apert and normal samples; also included are total shape change magnitudes ($\bar{t}$)

Landmark	Age interval, years			
	1–4	4–6	10–13	14–17
Apert				
NAS	0.098[A]	0.028	0.047	0.078
NSL	0.055	0.027	0.026	0.023
ANS	0.081	0.045[A]	0.032	0.051*
IDS	0.101	0.087[A]	0.077	0.079
PNS	0.177	0.110	0.086[A]	0.102*
PCP	0.122	0.078[A]	0.048	0.059*
SEF	0.082	0.104	0.066	0.066
SBAF	0.060	0.054*	0.020	0.048
PSL	0.150	0.196*	0.120*	0.095
SBNS	0.054	0.066	0.040	0.043
BAS	0.094	0.021*,[N]	0.100*,[N]	0.118*
CRU	0.060	0.028	0.044*	0.048
CPNC	0.074	0.035	0.061*	0.061
$\bar{t}$	0.093	0.068	0.059	0.067
Normal				
NAS	0.057	0.035	0.048	0.070
NSL	0.038	0.018	0.021	0.028
ANS	0.080	0.030	0.028	0.033
IDS	0.130	0.045	0.056	0.052
PNS	0.160	0.067	0.043	0.038
PCP	0.112	0.040	0.029	0.021
SEF	0.064	0.061	0.057	0.077
SBAF	0.065	0.026	0.025	0.039
PSL	0.136	0.107	0.114	0.106
SBNS	0.052	0.035	0.048	0.051
BAS	0.091	0.059	0.048	0.058
CRU	0.045	0.029	0.019	0.025
CPNC	0.056	0.026	0.022	0.035
$\bar{t}$	0.084	0.044	0.043	0.049

See table I for abbreviations of landmarks. *p = 0.05: intersample mean difference significant.

[A,N] Intersample variance difference significant (p = 0.05); initial indicates sample in which variance is larger: A = Apert; N = normal.

Significant differences in variance of the two samples are never present at more than 3 (23%) of the landmarks in any of the age intervals studied. None of the landmarks show significant differences in variance in more than one of the age groups studied and variation in size change magnitude is never different from normal local to 9 (69%) of the landmarks considered. Of the statistically significant differences in variances, all are due to larger variances in the Apert sample.

Statistically significant differences in mean magnitudes of size change due to growth never occur local to more than 3 landmarks (23%) during a given age interval, and there

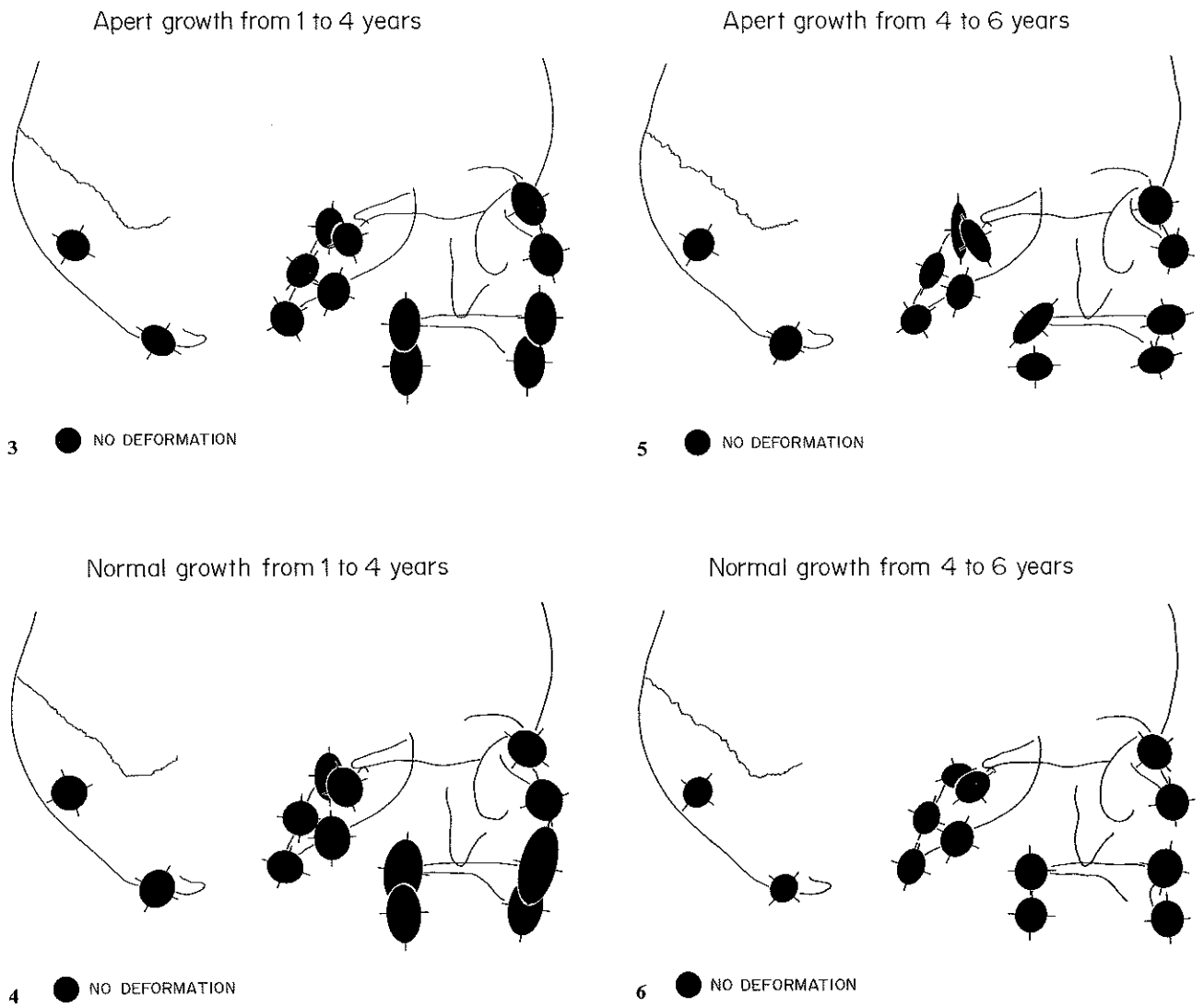

Fig. 3–6. Local morphological change resulting from the deformation of average younger to average older forms in two age intervals. Deformation refers to the two-dimensional change in shape and size local to each landmark as calculated from components of the form change tensor, and is considered representative of growth. The influence of nonlocal changes (rigid body motion) is not considered. To allow comparison across all age intervals and samples, the cranium depicted is the Bolton standard 4-year-old form [Broadbent et al., 1975] and principal values which determine the lengths of the vectors are corrected for the number of years in the age interval.

are no significant differences in size growth between the normal and Apert samples from 4 to 6 years. Only 1 true biological landmark shows significant differences in size growth during more than one age interval (cruciate eminence, age 1–4 and 10–13 years). Growth local to the cruciate eminence and constructed point on the neurocranium in the Apert sample is negative during the age interval 10–13 years, meaning that these localities actually decrease in size at this time. Although this pattern is significantly different from that seen in normal boys at this age, negative size change magnitudes are experienced local to the neurocranium (cruciate eminence, constructed point on the neurocranium) by Apert and normal boys from age 14 to 17 years. In both samples, these negative size change values reflect remodeling episodes which reduce the area of element 5. Ignoring statistical significance, 69% of the size change magnitudes reported in table II for the Apert sample are smaller than normal.

Shape Change. The average of local shape change values, the results of F tests for differences in sample

variances and those of t tests for differences in sample means are presented in table III. Landmarks located on the palate (anterior nasal spine, intradentale superior, palatal constructed point) and basion show significant intergroup variance differences from age 4 to 6 years. The variance of shape change local to the basion is significantly different from normal in the two middle age intervals considered, both due to increased variance in the normal sample. All other variance differences are due to increased variance in the Apert sample.

Significant differences in the magnitude of shape change due to growth are absent in the youngest age interval. Growth from age 10 to 13 years in Apert individuals involves local shape change magnitudes which are approximately twice those experienced by normal individuals. Shape change in Apert individuals from age 14 to 17 years is significantly greater than normal local to 4 landmarks (anterior nasal spine, posterior nasal spine, palatal constructed point, basion). Ignoring statistical significance, 79% of the Apert shape change magnitudes are greater than normal.

Directions of Growth. The results of t tests for mean differences in directions of growth between normal and Apert individuals (after rotation to a common coordinate system and transformation of the transformed y coordinate to a z score) indicate few significant differences ($p < 0.10$). Significant differences in direction of growth local to the landmarks used in analysis can be summarized as follows according to age interval: 1–4 years: anterior nasal spine, palatal constructed point; 4–6 years: nasion, anterior nasal spine, intradentale superior, sella floor; 10–13 years: basion, constructed point on neurocranium; 14–17 years: nasion, sella floor.

Figures 3–6 represent deformations of the average forms for the given age intervals and demonstrate the interplay of direction and magnitude of morphological change in the description of growth patterns. The comparison of figures 3 and 4 reveals an obvious intersample difference local to the anterior nasal spine. The ellipses local to this landmark differ in size between the samples, but because the difference between the length of the principal axes is nearly equal in each ellipse, the magnitude of local shape change is similar in both samples. Differences in local size change during growth in this age interval produce a shortened Apert palate in the anteroposterior direction as well as a shortened Apert midface in the superoinferior direction.

Local patterns of growth from 4 to 6 years are diagrammed in figures 5 and 6. The directions of growth for Apert individuals differ visibly from normal local to the anterior nasal spine, intradentale superior and posterior nasal spine. The magnitudes associated with these directions in the Apert sample would fail to increase facial height. Notable intersample differences in shape change occurring during growth are noted local to the pituitary fossa in the Apert sample, suggesting the local dynamics responsible for the extreme dysmorphology of this region in Apert individuals as described by Kreiborg et al. [1976] and Kreiborg [1986]. Intersample differences in principal directions and magnitudes of form change local to these and other cranial base landmarks during this age interval suggest the growth kinematics that produce the shortened posterior cranial base and platybasia reported in Apert individuals [Kreiborg et al., 1976; Kreiborg, 1986].

Discussion

We know from morphometric analyses and simple observation that Apert individuals are characterized by a distinct abnormal craniofacial morphology. The purpose of this study has been to explore the role that growth patterns play in the production of this dysmorphology. Tables II and III provide an impression of Apert growth in which localized size change magnitudes are generally less than normal, while local shape change magnitudes are greater than normal. Statistically significant intersample differences in growth are infrequent, however. It appears that if abnormal postnatal growth patterns are responsible for producing the characteristic Apert craniofacial morphology, it is a process which focuses on distinct localities differentially over time.

Postnatal growth in Apert individuals may differ from normal at loci other than those considered here, or in the third (mediolateral) dimension. Three-dimensional analyses of alternate structures can increase our understanding of growth in Apert syndrome. Developments in imaging technology provide appropriate data for three-dimensional FES analysis of craniofacial growth. Analyses using computed-tomographic images are already underway [Richtsmeier et al., 1988].

This study has demonstrated the potential role that FES can play in defining the growth kinematics which produce the forms we observe. In the study of growth, the strengths of the FES method lie in its ability to define directions and magnitudes of form change local to specified landmarks without reference to a particular orientation scheme. FES is likely to provide new answers to old questions of biological form and its variation.

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