

CURRENT TOPIC

Short term growth: rhythms, chaos, or noise?

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Non-linear growth

It has been traditional to think of height gain of children as a steady process and the term 'linear growth' is often used as shorthand for increase in stature as opposed to weight.¹ We are often reminded of this with simple graphics on textbook covers and logos for organisations and meetings that depict a series of children of different heights with their heads connected by a smooth line. It is also easy to believe that the beautiful curves on a centile chart² describe the real progress in height of an individual, without realising that the chart is a statistical construct from population data that often has been 'smoothed' mathematically to produce the finished product.

Paediatricians normally monitor the growth of their patients at relatively infrequent intervals, and for relatively brief periods of the child's growth span. At this level the healthy child will tend to follow a centile channel determined (after the first two years of life) by his or her genetic background. Indeed the growth of an individual approximates to a series of curves which can be described mathematically as an exponential (infantile growth) plus a second degree polynomial (mid-childhood growth) plus one of a family of logistic functions (a description of the timing of puberty and then cessation of growth). This is the basis of the infancy-childhood-puberty or ICP model of growth^{3,4} but it must be remembered that this is both a *model* of growth and an *approximation* – not a description of real life.

If we assess the growth of an individual by multiple measurements over a long period of time then deviations from a smooth curve become apparent. Montbeillard's son is the classic example – the Count demonstrating that there was apparently periodic acceleration and deceleration in the growth rate of his child as early as 1777. Some of these were associated with the season of the year, others were unexplained.⁵

The more closely we look at the growth process the more non-linear it becomes. Indeed if we think about the process that leads to an increase in height there is no reason to suppose that linearity is anything other than a convenient approximation to reality. First picture a single cell in a growth plate: at any time it may be resting, synthesising, or dividing as it passes through the cell cycle. In the simplest possible system of one cell exposed to a single growth factor with feedback regulation, given a response that

is not instantaneous there would be a simple oscillation of division and rest with reciprocal peaks and troughs of the growth factor – the net result being 'growth' which would be predictable but non-linear. Then complicate the system by adding multiple cells, arranged in thousands of columns per growth plate. Each cell is under the control of multiple hormones and growth factors secreted in an endocrine, paracrine, and autocrine fashion. The endocrine events are modulated themselves by catabolism, daylight hours, time of day, and pulse generators in the central nervous system. Other factors such as temperature, nutrient supply, and pressure (in an erect human) also modulate cellular events. The control mechanisms for division and synthesis are different at each stage of the cells' differentiation in the growth plate. Then realise that there are at least 58 epiphyses between the heel and the top of the head, not all responding to any of the aforementioned signals in the same way⁶ or contributing the same amount of growth to final height. The multiple small events throughout the body all summate, but growth cannot be a linear process.

We then come to the measurement of growth itself. All measurements are themselves approximations and subject to equipment and observer error. There have been many attempts to refine anthropometric^{1,7-9} or biochemical observations¹⁰ to predict subsequent growth, either natural or as a consequence of treatment. It may be that the development of ever more precise measurement techniques and devices will merely lead to the observation of more and more detail of the growth process, interesting in itself, but of no help in prediction of later growth.

The study of dynamic interacting systems, of which human growth is but one example, takes us into the realms of chaos theory.¹¹ Deterministic chaos is the random looking and unpredictable output produced by the effects of different modifiers, any of which can be described by simple rules, on a single non-linear system. It is characterised by 'periodicities' and 'intermittencies' where small events summate to produce wild swings (or saltations?) in the observed value. Chaotic systems are also characterised by 'phase shifts', where there can be sudden changes from one quasistable consequence of summated events to another (one could stretch a point and suggest a parallel with the changes seen at the

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interface between infancy and childhood growth and childhood and pubertal growth) and 'sensitivity on starting conditions' where small differences in the initial configuration of the system (child?) may produce extreme variation in the eventual output (height?).

To give a familiar example from the literature of chaos theory, which draws heavily on analogies with weather forecasting, the 'butterfly effect' states in simple terms that long term weather prediction is impossible as very small changes in the initial conditions can magnify to produce large variations at another point, or, if a butterfly flaps its wings in a rain forest this will perturb the 'starting conditions' and cause subtle local changes in air pressure that produce larger regional changes the net effect of which may be later storms over England. However, an identical butterfly on the next leaf with the next wing beat may produce no observable later weather effects, or tornadoes in Arizona. However, although precise prediction of next week's weather is not possible, we can say with virtual certainty that summer will follow winter. In a similar manner we may not be able to predict the exact height of a child three months from now but we can make broad predictions about a likely final height.

As one looks deeper into the processes of the chaotic system one continues to find apparent disorder at every level down to the subatomic quantum realm. If the disorder has short, medium, and longer term fluctuations that are similar in their appearance, demonstrating 'scale invariance', then this is called 'fractal' behaviour.^{11 12}

Chaotic systems are unpredictable, but the fact that short term unpredictability exists in human growth, and that height gain is non-linear, does not mean that it is necessarily truly chaotic. If a large number of independent sources of fluctuations interact on any process they may produce stochastic (that is, non-deterministic) noise. It may be that growth should be considered as a single non-linear system, when chaos theory might apply, but non-linear time series analysis of a huge number of data points ($>10^5$), impracticable in longitudinal human studies, is required to differentiate this from random noise.

We will now examine the methodology and some of the current knowledge of the short term growth process to see if any conclusions may be reached concerning the 'true' nature of childhood growth.

Measurement error

(1) HEIGHT

Height is the most reliable of classical anthropometric techniques,^{13 14} but still a source of artefactual variations in height. This subject has recently been explored in detail by the Wessex Growth Study^{15 16} and measurement of height is still often performed very poorly.¹⁷ Details of the means of analysing machine, interobserver and intraobserver error can be found in the chapter by Noël Cameron in *Human Growth*.¹⁸ It is unfortunately still rare for researchers to quote these values in relation

to their observations (this is especially true for that deceptively simple measurement, weight). If one's measurement error exceeds the likely value of the change in the parameter observed, then there is no point in making the measurement or drawing conclusions about the changes you may observe. This should be borne in mind when considering treatment responses in height velocity measured over short periods where these values are not available.

Distinctions must be made between community based surveys for short stature and the more precise growth studies that are possible using selected subjects in a measuring laboratory. Voss *et al* detail error due to equipment malpositioning and child based factors,¹⁵ besides observer error that will be magnified still further if more than one measurer is used. One may be reasonably confident that a single height observation may be accurate to ± 2 SD, equivalent to ± 0.5 cm in many community based studies. This is approximately the increment in height one might observe over 2 months in mid-childhood, and more frequent measurements are unlikely to be of value.

We are lucky in Sheffield to have had two consecutively employed professional auxologists who have made observations on high quality equipment in a specialised measuring laboratory over the last 20 years. It has been their practice to take measurements of height without knowledge of previous records, to avoid bias. Possibly more important than the technique are the subjects used in the short term growth studies quoted below, who are 'trained' to be 'good' subjects by multiple attendances. The mean SD of measurement of our current auxologist, performing a series of completely blind replicate measurements on these individuals is 0.11 cm, equivalent to the increment of height observed in approximately four weeks.

Postural changes in height through the day, largely due to spinal disc compression, have been quantified since the 18th century. The Reverend Wasse demonstrated that height loss through the day could be as much as 6/10ths of an inch, came from the back not the legs, and was more prominent in younger people and heavy labourers.¹⁹ Montbeillard showed that his son 'shrank' after an all night party.⁵ These postural losses have been quantified as 0.55 cm and 1.2 cm by different 20th century observers^{20 21} and can be minimised, but not eliminated by use of the 'stretch' technique²² where the mean morning difference was 0.2 cm and 0.46 cm through to the afternoon. It is thus important that short term growth studies should try to measure children at the same time of day, wherever possible. The often quoted phrase to medical students 'you can lose weight but you can't lose height' is not true at this time scale.

(2) HEIGHT VELOCITY

If one considers height velocity the possibility that measurement error contributes

significantly to one's observed results increases dramatically. Meredith estimated the maximum frequency of measurement from the 90th centile confidence limits of calculation of velocity for a number of parameters.¹⁴ He estimated that bimonthly measurements in mid-childhood would yield acceptably accurate results given an error of measurement similar to that found by Voss *et al.*¹⁵ The more rigorous 95% confidence limits of a velocity in cm/year calculated from two measurements a year apart is ± 2 multiplied by the SD of the measurement multiplied by the square root of two. The same limits for a velocity calculated over three months is $\pm (2 \text{ SD} \times \sqrt{2}) \times 4$ and at a two months gap $\pm (2 \text{ SD} \times \sqrt{2}) \times 6$. Given our observational accuracy of 0.11 cm a change in velocity of $> \pm 1.8$ cm/year would have to occur over an eight week period to be reasonably sure that it was a real event.

Short term growth measurements in childhood

(1) HEIGHT

Given these constraints, what does growth in height look like when studied at this detail? We have analysed the records of a number of children attending a specialist clinic for cystic fibrosis in whom measuring laboratory heights collected as detailed above are available, taken at approximately the same time of day, over a long period, at approximately eight week intervals. It must be stressed that the reason we have such detailed measurements available is that these children are *not* normal healthy individuals – although in the example cited below the health of the child is remarkably good – but it is still possible to make some inferences about the growth process if one assumes that catabolic events will be over represented.

Figure 1 shows the height chart and fig 2 the height velocity for one such child measured at yearly (two points, one year apart), six monthly (two points, six months apart $\times 2$), three monthly (two points, three months apart $\times 4$), and using all available data (mean interval eight weeks). One can appreciate an increasing complexity of changes in height velocity as the measuring interval decreases. Even ignoring changes of less than ± 1.2 cm/year at three months, or ± 1.8 cm/year at eight weeks as possibly being artefacts of measurement error, there are surprising variations in height velocity. This pattern would be familiar to stock market analysts, and superficially seems to demonstrate scale invariance, in other words growth rate appears to show some attributes of fractal behaviour. Superficial analysis of this data shows no obvious rhythmicity or seasonal changes in rate, but mathematic techniques beyond the power of these authors, and several orders of magnitude more data points are required to 'prove' chaos.

Larger scale variations in height velocity have been described with season of the year. These changes are not present in all members of a population,²³ can be in different phase in a

similar population at different times,²⁴ and are reduced in relationship to blindness²⁵ but not reduced daylight hours.²⁶ Seasonal variations are even said to persist in growth hormone treated children.²⁷ Careful analysis of height velocity in Edinburgh children shows a series of growth spurts through childhood,²⁸ some of which may be seasonal and others which may represent the mid-childhood growth spurts that have been observed in other studies.^{29 30} Seasonal changes even occur in human hair growth, but not in that of fingernails!³¹

One study that exemplifies all the above points comes from Japan.³² Two observers measured their children daily for a year. Daytime variation in height, due to spinal compression is clearly seen. The children show steady growth of subischial leg length at two different rates in the observation period. The back grows hardly at all for the first part of observation, but suddenly grows at a rapid rate in the last two months, resulting in a leap, or saltation, of height.

(2) ISOLATED AREAS OF SKELETAL GROWTH AND KNEMOMETRY

Further information on the growth process can come from observations made on single bones or well defined groups of bones or other tissues. A number of radiographic studies on bone growth have been made in humans.³³ Over a period of years around puberty, Roche showed that the maximum increment in length of the radius and tibia had different relationships to the peak height spurt.⁶

Measurement of short term growth in stable aggregates of bones began with ulnar condylography⁷ but evolved into the measurement of the lower leg as knemometry. We have found knemometry in children to be precise (mean coefficient of variation of measurement 0.09%) and observer independent.¹ The lower legs of healthy children appear to grow at a steady rate then show unexplained leaps in growth. There are also clear slowings or shrinkage that can be associated with even minor catabolic stress, followed by catch-up growth. Shrinkage here is presumably due to compression of non-growing bone and cartilage and a possible shift in the balance between bone deposition and resorption with illness that can account for the growth arrest or Harris' lines seen on plain radiographs. Hermanussen *et al* have studied the periodic growth in healthy children in most detail.³⁴ They describe 'mini-growth spurts' and by analysis of a rolling height velocity ascribe a periodicity of 30–55 days to this phenomenon. The analytical technique used is, however, prone to a mathematical effect called aliasing³⁵ which can produce regular periodicity where none exists and will mask short term phenomena.

Radiographic and knemometric observations suffer from the fact that the growth behaviour of only a single part of the skeleton is analysed. Non-linear behaviour is likely to exist in other areas, however, and it is very unlikely that the periodicities would cancel out to produce smooth growth in stature.

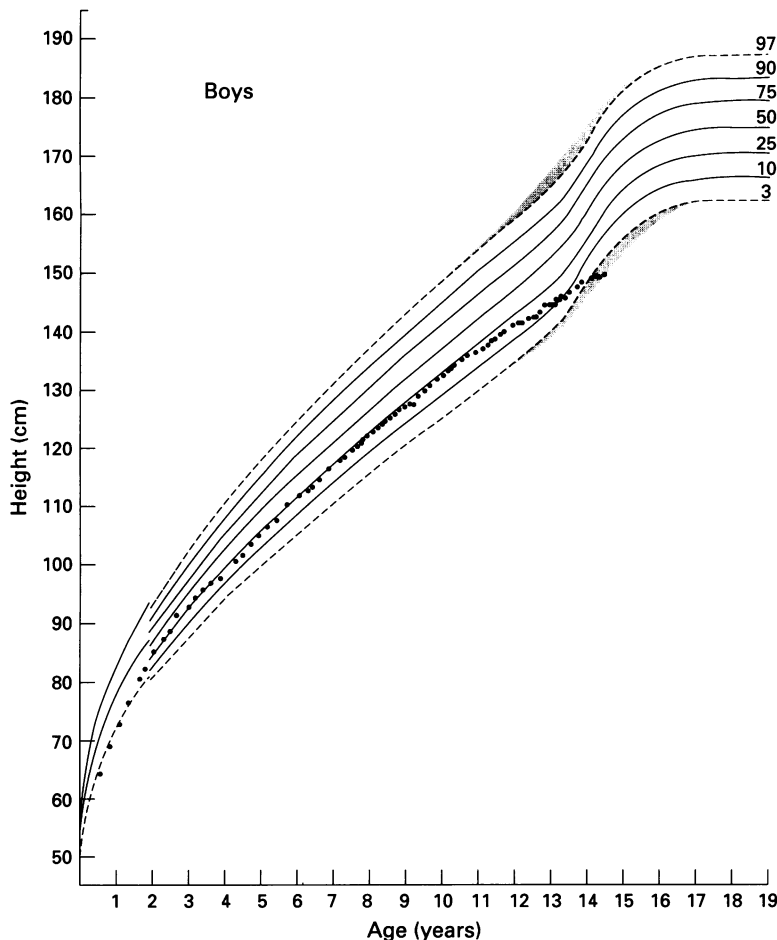


Figure 1 Growth of subject plotted on height chart of UK Tanner and Whitehouse 1975 standards; adapted from Castlemead Publications, Welwyn Garden City, 1983 (shading indicates limits for single occasions).

Short term growth measurements in infancy

(1) WHOLE BODY

Periodic changes in weight gain have been described in neonates.³⁶ The phenomenon of 'fractal' changes in weight gain is clearly seen with decreasing measurement intervals.

By using a modified length measuring device, Lampl and colleagues describe growth in length of the post-term infant as a process of saltations (leaps) interspersed with long periods of stasis.³⁷ Similar data also exists for ultrasonically estimated leg length of fetuses (M Lampl, P Jeanty, M L Johnson. *Saltatory growth patterns in fetal tibia*; personal communication). In these cases data has been analysed by various mathematical models and the saltatory model provides the 'best fit' through the data points. Again this does not necessarily represent the actual growth of the leg; as we have previously discussed chaotic or complex behaviour is prone to show intermittencies. Apparent saltations can also be a consequence of growth rate exceeding the measurement error of an observation.

(2) KNEMOMETRY

The neonatal knemometer, first described by Michaelsen *et al*,³⁸ has been used by us to measure a large number of premature neonates. It is also precise, mean SD of

measurement 0.3 mm, but unlike the bigger knemometer, highly dependent on the use of an experienced observer. Soft tissue changes, using the technique as described have very little effect on the observations,⁸ we have even observed leg growth in a hydroptic infant who lost 30% of his birth weight as fluid in the first three days of life (unpublished observations). As in older children 'negative' growth, or shrinkage, may occur, especially at times of catabolic stress. Here the bone is not compressed, as the infants are nursed supine, but again presumably reflects a change in the balance of bone resorption over deposition. The precision allows for observations of leg growth liable to occur over 2–3 days. We have used it to explore the effects of chronic lung disease, nutrition, and steroid treatment in this group of children.³⁹ Long term observations on the growth of 'healthy' premature neonates are, by definition, scarce. We have analysed the leg growth of one 28 week gestation infant who was free of any complications of prematurity and kept on our unit for 63 days pending adoption. Only one change in management was made, the institution of low birthweight formula from day 18 to day 46. Changes in rate of leg growth are shown in fig 3. At 6–7 day increments there was an association between changes in weight and changes in leg length that was less clear when analysed at 2–3 day increments. Most of the changes in leg growth

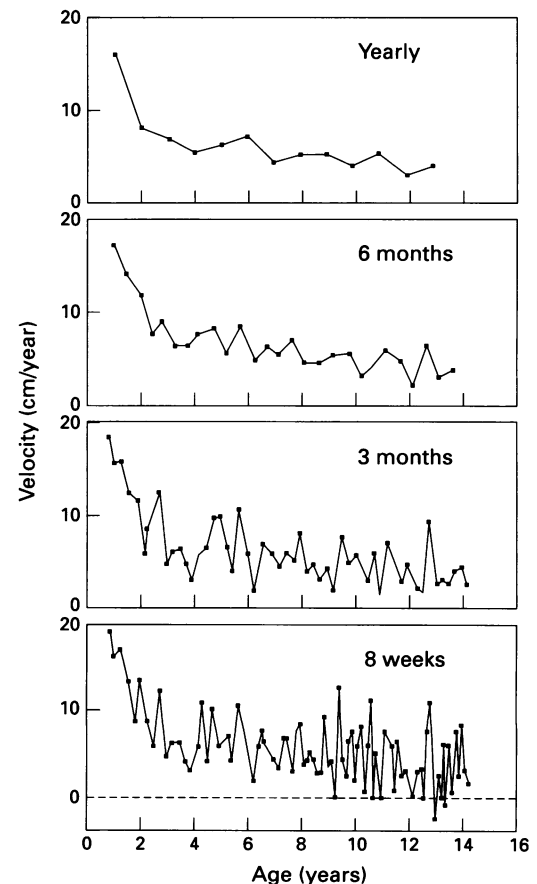


Figure 2 Height velocity of subject plotted at yearly, six and three monthly, and at approximately eight week intervals for 14 years. The total number of observations was 89 with a mean (SD) measurement interval of 8 (3) weeks (range 2–17 weeks).

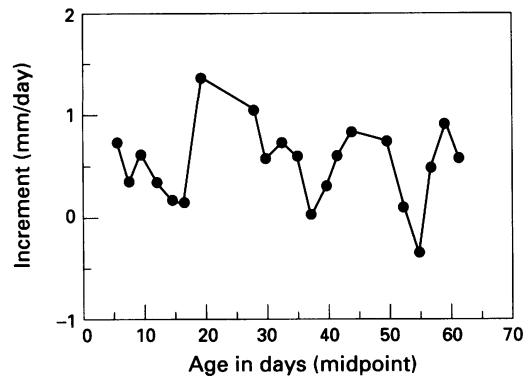


Figure 3 Two or three day leg length increment measured by knemometry in healthy 28 week gestation infant from birth to 63 days. Low birthweight formula feeds were instituted on day 18 and discontinued on day 46.

velocity exceed the error that can be attributed to measurement error and derivation of velocity (± 0.25 mm day) and show non-linear behaviour with a clear positive effect of the introduction of low birthweight formula. Bishop *et al* demonstrated a similar phenomenon over a much shorter period, after initial weight loss, in a group of 45 term infants.⁴⁰

Animal models

Using tetracycline staining of rabbit bones exposed to controlled lighting conditions Hansson *et al* showed that there were distinct periods of rapid and slow growth throughout the day.⁴¹ This is in contradistinction to observations of high accuracy (error of measurement 0.05 mm day) using metal pins inserted into rabbit bones growing at 0.27 mm day which failed to show saltation, but revealed a Gaussian distribution of velocities around an intermediate value, more indicative of continuous growth than a periodic model.⁴² Individual growth patterns were clearly non-linear, however.

Conclusions

There is mounting evidence that growth in height is not a steady process, but made up of intermittent episodes of growth that may occur in different parts of the skeleton at different times. Growth rate is determined by a complex interaction of physical, endocrine, nutritional, and anabolic effects and may be disrupted by ill health and psychosocial factors.^{1 43} Measurement error and postural change of standing height may produce apparent changes in growth velocity, but even when these are accounted for there appears to be evidence of non-linearity both at the whole body and single bone level. It is important to realise that this non-linearity defeats any attempts to predict long term growth from short term observations either of one bone or the whole body,^{23 44-46} and this should no longer be attempted.

Short term growth studies may have their value in describing the dynamics of growth and, in well designed research with adequate follow up, comparing two growth suppressing or promoting treatments.⁴⁷

Beware of drawing too many conclusions from the fit of mathematical models, including chaos theory, to data. The ICP model has been interpreted as showing relative independence of growth from the influence of growth hormone in infancy,^{3 4} but real life observations on hypopituitary infants show this not to be the case.⁴⁸

A single non-linear simple dynamic system with interacting control mechanisms will tend to produce a chaotic pattern. A large number of independent sources of fluctuation on any process will produce unpredictable noise. Differentiation of the two processes with respect to childhood growth is not currently possible. We cannot predict an individual's exact height six months from now in the same way that we cannot predict the weather in a weeks' time. This article has been designed to be speculative and thought provoking and to show that growth is complex, at least in the short term. Possibly by providing more questions than answers it demonstrates that much further research remains to be performed.

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