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Intra-Individual Variation in Energy Requirement and its Genetic Significance[1]

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SUMMARY

It is generally assumed in nutrition studies that the energy requirement of an individual is fixed and that any variation from day to day is negligible relative to variation between individuals of the same age, sex and body weight. However, this assumption does not find support in the available data and on the contrary, the requirement in an individual is found to vary over time. This variation is found to persist even when data are averaged over a week. Further, the requirement follows a stochastic stationary distribution implying that as man advances in time, the genetic entities possessed by him interact with the environment to keep the variance constant. An attempt has been made by the authors to relate the genetic component due to this interaction with the auto regulatory mechanism. It has been found that the strength of this interaction can be measured in terms of the serial correlation coefficient signifying the degree of auto-regulatory mechanism.

Key words: Intra-individual variation, Energy requirement, Genetic × Environment interaction, Auto-regulation, Intra-individual heritability.

1. *Introduction*

Edholm *et al.* [1] provided the first opportunity to examine the source, size and nature of intra-individual variation in energy requirements. These data were subsequently re-analysed by Sukhatme [5], who found that the variance does not decrease inversely as the size of the period, but decreases slowly and even stabilises. It was also found that successive observations are correlated and the daily requirement could be considered as distributed in a stochastic stationary distribution of the Markov type. This study leads to the conclusion that if intra-individual variation is a fundamental source of a variation, it is because the variation over time appeared to stabilise as the period of observation increased from 1 to 5 days. This can be interpreted to mean that as the individual

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advances in time, he becomes a different individual which is, of course true, as the specialised environment in which he is being brought up apparently interacts with the genetic component to keep the variance constant. The concept of heritable variance can be extended to apply to observations on the same individual to isolate and evaluate the interaction between genetic and environmental component to account for the constancy of the intra-individual variation. Sukhatme and Narain [9] examined the implications of the intra-individual variation in energy requirement using Edholm's data. In this paper, these aspects are discussed and illustrated the significance of intra-individual variation. We welcome such efforts particularly involving data from developing countries such as Iran.

2. *Intra-Individual Variability*

The data collected by Edholm *et al.* [1] involved simultaneous observations on energy intake and expenditure on 35 young army recruits during the 2nd, 5th and 8th week of a nine-week period of training at 6 different Depot Centres in the UK, using the most sophisticated techniques of measurement yet developed. During weekdays, the subjects were engaged in similar activities of group nature such as drill, lectures, meals and games. The energy intake of the subjects was measured using the weigh as you eat method from a common table and expenditure was calculated by timing activities and from energy

Table 1. Analysis of daily energy intake and expenditure in kcal/kg of body weight in Depot Centre D

(Period : Monday to Friday)

	d.f.	Mean square		Estimates of true variance	
		Intake	Expen-diture	Intake	Expen-diture
Between subjects	5	788	37	37	–
Between weeks within subjects	12	230	58	22	4
Between days within weeks	72	122	36	122	36
σ_w		12		6	
Mean		61		60	
% C.V.		20		11	
Var. of mean		46		11	
% S.E.		11		6	

expended during each activity as estimated from the amount of oxygen consumed using Integrated Motor Pneumotacho-graph (IMP) devised for the purpose. The examination of data showed that intake varies much more than expenditure from day to day at the various centres. The cumulative energy balance at the end of week (period) was very large and varied considerably from one period to another. Table 1 gives analysis of variance of the data on daily intake and expenditure at one of the centres viz. Depot Centre D for the period of five days from Monday through Friday. The observations are expressed on per kilogram body weight basis.

Let σ_b^2 stand for the true variance between subjects, σ_p^2 for true variance between periods within subjects and σ_d^2 for true variance between days within periods within subjects. Then the expected values of the three Mean Squares in the hierarchical model of ANOVA would be :

$$\begin{aligned} &\text{E (between subjects within Depots)} = 15\sigma_b^2 + 5\sigma_p^2 + \sigma_d^2 \\ &\text{E (between weeks within subjects)} = 5\sigma_p^2 + \sigma_d^2 \qquad (1) \\ &\text{E (between days within weeks)} = \sigma_d^2 \end{aligned}$$

where the numbers preceding σ_b^2 and σ_p^2 represent the number of days observed for each subject and during given period. It follows that the variance of a single observation for any subject is given by

$$\sigma_w^2 = \sigma_p^2 + \sigma_d^2 \qquad (2)$$

and that of the mean intake and expenditure per kg of body weight over p days by

$$\sigma_p^2 + \sigma_d^2 / p \qquad (3)$$

It will be seen from Table 1 that the mean square between periods is significantly larger than mean square between days within periods. This indicates that the variance of the mean of p values stabilizes at σ_p^2. The CV of daily intake is seen to be 20 percent. If day to day variations were random, the CV of mean daily values over time in the same individual would be smaller. The data show that it is not.

Unlike intake, the variation in the case of energy expenditure is smaller. The CV for daily expenditure is 11 per cent and that of the mean daily expenditure is 6 per cent. The smaller magnitude of the CV in the case of energy expenditure is to be expected since the army recruits were engaged in fixed tasks from day to day, but they had choice of intake on all days. This analysis refutes the assumption that expenditure in an individual maintaining body weight and engaged in similar activities from day to day is constant and is equal to individual's habitual intake. This suggests that body regulates its energy balance on a range of intakes by varying the efficiency of intake utilisation.

3. *Auto-Regulatory Nature*

The series of Edholm *et al.* [1] referred to earlier relate to 3 non-continuous weeks and therefore does not permit a direct study of auto-correlation to prove that energy requirement is self-regulated over a range of intakes much in the same manner as the series of daily nitrogen balance in man living on fixed level of nitrogen and maintaining body weight as studied by Sukhatme and Margan [6]. The mathematical model for such an auto-correlation, however, can be indirectly verified by computing variances of the mean balance, when daily balance is averaged over 2, 3 or more successive days. The results of this exercise are given in Table 2. It is found that the variance of the mean balance does not vary inversely as the length of the period, but that it decreases slowly, thus confirming that successive values are serially correlated. Further, the hypothesis that the daily balance is distributed in a stochastic stationary

Table 2. Variance of individual's mean energy intake, expenditure and balance based on p successive days as proportion of unit variance for p=1 in Depot Centre D

Period (days)	Observed			Expected	
	Intake	Expenditure	Balance	ρ=0.00	ρ=0.30
1	1.00	1.00	1.00	1.00	1.00
3	0.43	0.63	0.55	0.33	0.49
4	0.27	0.37	0.31	0.25	0.39
5	0.28	0.29	0.29	0.20	0.32
6	0.21	0.32	0.25	0.16	0.27

manner of the same Markovian type with serial correlation of the first order equal to 0.3 seems perfectly plausible. Edholm's data must, therefore, be interpreted to mean that although intake may not be equal to expenditure even when averaged over a week, man is in balance every day in a probabilistic sense with varying intervals between peaks and troughs and varying amplitudes in daily balance.

4. *Genetic Significance*

Sukhatme and Narain ([7], [8]) showed that the intra-individual variability in calories or protein intake is enhanced due to interaction between the genotype of the individual and the environment as he advances in time. Theoretically, the situation is best handled by invoking a model for the one-way analysis of variance with correlated errors.

Assuming that we have data on energy balance for k subjects recorded at successive n days, the model describing the response of subject i on t-th day is given by

$$Y_{it} = \mu + b_i + w_{it} \tag{4}$$

where Y_{it} is the corresponding response with μ as overall mean, b_i's are independently and identically distributed with variance σ_b^2, independently of w_{it} and w_{it}'s for the same individuals, are n consecutive random variables following an auto-regressive process of order one as described earlier . They have shown that the variance of the mean of the individual when averaged over n different days can be expressed as

$$V_{P(n)} = \sigma_b^2 + \bar{r}\,\sigma_e^2 + [\,(1-\bar{r})/n\,]\;\sigma_e^2 \tag{5}$$

where $\bar{r}$ is the average correlation between observations of a given individual. It is related to ρ, the serial correlation of the auto-regressive process.

The effect b_i in the above model reflects genetic effects of the i-th individual as well as certain environmental effects permanently associated with the individual's development such as intra-uterine and external environment experienced by him. Its variance would therefore contain the genetic component of variance (V_G) as well as common environmental component of variance V_{E_g} so that

$$\sigma_b^2 = V_G + V_{E_g} \tag{6}$$

In so far σ_e^2 is concerned, it reflects only the variability due to local environmental effects V_{E_s} provided the genotype does not interact with the environment. If it is not so, another component of variance due to the interaction V_{GE_s} would enter in the within-individual component so that when the observations are averaged for several days, it does not bring about the reduction in the variance of the mean of the individual to the extent it would do if the genetico-physiological process of calorie metabolism has been the same on each day. We, therefore, get

$$\bar{r} = \left(V_{GE_s}\right) / \left(V_{E_s} + V_{GE_s}\right) \tag{7}$$

The average correlation $\bar{r}$ can then be given a genetic interpretation as *heritability of the individual or intra-individual heritability* in a manner similar to the concept of heritability. It is the fraction of the total intra-individual variability which is due to interaction between the genotype and the environment and could take any value between 0 and 1. The existence of the genotype x environment interaction thus enhances the intra-individual variability with stabilisation of variance as we increase the period of time over which the data are collected. The strength of this interaction can be measured in terms of the serial correlation coefficient signifying the degree of auto-regulatory mechanism.

As shown in Narain [4], the above considerations can be also extended to consider covariance between relatives so as to reveal how genetic relationship controls the auto-regulatory mechanism measured in terms of ρ. It can be shown that compared to the average correlation in the given generation $\bar{r}$, the average correlation ($\bar{r}^*$) in the relative with a genetic relationship r_g takes the form

$$\bar{r}^* = \left(r_g V_{GE_s}\right) / \left(V_{E_s} + r_g V_{GE_s}\right) \tag{8}$$

One can then relate the two as

$$\bar{r}^* = (r_g \bar{r}) / (1 - (1 - r_g)\bar{r}) \tag{9}$$

where r_g is 1 for identical twins, (1/2) for parent-offspring or full-sibs and (1/4) for half-sibs. Thus as $\bar{r}$ increases from 0 to 1, $\bar{r}^*$ also increases characteristically between 0 to 1, depending on the value of r_g. At a given value of $\bar{r}$, the value of $\bar{r}^*$ is highest i.e. equal to $\bar{r}$ for identical twins and lowest for half-sibs.

If follows from above that

$$\sigma_p^2 = \bar{r}\,\sigma_w^2 \tag{10a}$$

$$\sigma_d^2 = (1 - \bar{r})\,\sigma_w^2 \tag{10b}$$

and that as a consequence, one can write for the variance of the mean of p days in an individual the expression

$$\sigma_w^{2*}\ [\bar{r} + (1 - \bar{r}) / p] \tag{11}$$

where σ_w^2 is starred to distinguish it from σ_w^2 in the uncorrelated case. The intra-class correlation $\bar{r}$ can be approximated as

$$\bar{r} = 2\rho / (p-1)(1-\rho) \quad (12)$$

Substituting in equation (11) we get for the variance of the mean

$$[(\sigma_w^{2*} / p)] [(1+\rho) / (1-\rho)] \quad (13)$$

When ρ is zero, we have the familiar expression for the variance of the estimated mean as

$$\sigma_w^2 / p \quad \text{replacing} \quad \sigma_w^{2*} \text{ by } \sigma_w^2$$

Introducing inter-individual variability one may, therefore, write for the variance of the mean :

$$\sigma_b^2 + (\sigma_w^{2*} / p) [(1+\rho) / (1-\rho)] \quad (14)$$

In terms of the genetic/environmental components, this becomes :

$$\sigma_b^2 + (\sigma_w^{2*} / p) [(1+\rho) / (1-\rho)] \quad (15)$$

+ variance component due to environment

The enhanced variability that we observe in mean daily intake in the same individual can thus be explained in two ways : (1) in terms of auto-correlation of order 1, with its implications for regulation, and (2) in terms of intra-class correlation $\bar{r}$ with its implication for genetic significance as described above. It would appear that the capacity to adapt within the threshold limits is heritable, and implies adaptive regulation.

The estimates of intra-class correlation ($\bar{r}$) and of serial correlation of order one (ρ) in daily energy intake and expenditure in kcals/kg of body weight in Depot Centre D are :

	Energy	
	Intake	Expenditure
$\bar{r}$	0.15	0.10
ρ	0.23	0.17

The heritable portion of the variance arising from interaction with environment is admitedly small being of the order of 0.15 for intake and 0.10 for expenditure. Although small, the resulting value of the auto-correlation is consistent with the hypothesis of auto-regressive model of order one advanced earlier. The small size need not detract from its value in explaining the cause of the persistent nature of intra-individual variation. In the nature of things $\bar{r}$ and with it ρ, are expected to be small when the main concern is to study the influence of day to day change on the performance of the next day within the frame-work of ontogenic growth. In other words, while the normal range of $\bar{r}$ will be $-1 / (p - 1)$ to 1, and the distribution skew, it will be even narrower and the distribution skewer in the short term phenomenon that is studied here.

It would thus appear that energy balance is under the physiological control of the body with different genes switched on and off on different days and periods of ontogenic development in response to specialised environment. It is because of this interaction that man is able to bring for himself a change in the rate of energy flow, speeding it sometimes and slowing it down on other occasions, to maintain *homeostasis*. No one can change the genetic blue-print with which one is born, but it appears that one can influence its development under the impact of sustained specialised environment. Although accounting for only a small portion of the total variance, this possibility has obviously far reaching implications for social, economic and cultural changes.

5. *Discussion*

It is shown in the foregoing that the interaction of genetic entities in man with the specialised environment is the cause of the enhanced variance. In nutrition literature, one talks of either genotypic or environmental variance, ignoring this interaction term. We have deviated from this practice and emphasised the importance of the covariance term in the variance of the sum of genotype and environmental effects over time in the same individual within the framework of onto-genic growth. We postulate that development of man, his intellect, his mind and his conscious thinking is made possibly by this covariance term. What one is today is due to the change resulting from the covariance term over and above what he was born with and inherited from his parents. This covariance term emphasises the importance of appropriate environment and education as a tool of achieving a way of life suited to our culture, needs and resources. In our view, we cannot talk of traits like intake or intelligence quotient (IQ) as wholly determined either by nature or nurture, ignoring the third component altogether. The intake is only under partial biological control and its heritable basis, appears to arise from the processes of perception in the unfolding of genetic code.

The hypothesis of interaction between nature and nurture is rather difficult to conceive. This is because we tend to believe that each of us is born with a fixed genetic code and therefore, genetically programmed to achieve the growth potential with adequate intake. That we cannot change the genetic code with which we are born is true. But that does not mean that the genetic potential for growth is fixed and is the same for all. The function of the genetic code is simply to direct the assembly of amino acid released from food in a precise sequence to make the protein that body needs. This is done by a sequence of three out of four nucleotides of deoxyribonucleic acid (DNA) which is the chemical substance of heridity, the gene being a segment of DNA. Although the precise sequence of amino acid is under the control of DNA, the number of proteins to be made and the time and conditions under which they are to be made are apparently not under the control of DNA. Experimental evidence shows that a large number of DNA sequences are never transcribed into messenger RNA ribonucleic acid which are intermediatory protein molecules for the transfer of DNA instructions to the protein it synthesises and suggest that it is the function of the information contained in the untranscribed DNA to control the speed of metabolism so that the body throws out disruptive forces of variation and assimilate the random variation into the pattern of hierarchical variation as part of man's progressive development. The data analysed and presented here confirm this hierarchical associative nature of intake in man engaged in fixed tasks. This is the reason why daily requirement is found to be dynamic and distributed with stationary variance. The variance of the energy requirement cannot therefore, decrease inversely as a length of the period but decrease slowly to a point where it assumes a stable value.

Repetition, variation and integration at each step of internal differentiation is the way man grows. This is how, for example, a child picks up speaking. He gropes for correct syntax and phonetics, gets it after many a trial and error and assimilates it. Man has an innate capacity to learn and to incorporate his learning experience into traces of hierarchical pattern. The intake is under partial biological control and therefore, is not hereditary in the same sense in which height or colour of the eyes are heriditary, but expression (10a) clearly shows that it has a heritable basis. Such a basis may be traced to cognitive faculties in man which are known to be served by billions and trillions of neurons and neural pathways in controlling the action of genes. Strictly speaking, we must await for empirical data from neurologists and psychologists to test this hypothesis. We look forward to such data and their analysis from developing countries particularly Iran. The fact that daily intake for given work output has a stationary variance implies that man can direct his daily intake in innumerable ways to correspond to stored neural messages. It is in this sense that man can be said to regulate his intake without modifying the germplasm. Mayr [3] describes it as gradual opening of the genetic programme permitting the incorporation of personally acquired experience.

When intra-individual variation in energy requirement is the fundamental source of variation and the successive values can be generated by an auto-regressive process such as Markov, it means that there is no absolute energy requirement for any day or period. It simply means that the individual is in homeostasis and that his requirement is controlled by a regulated system. Viewed this way, the intra-individual variation must be considered as reflecting man's capacity to regulate his intake, while maintaining his body weight and work output.

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