ACTA STEREOL 1987; 6/SUPPL II: 43–56
ISS COMMEMORATIVE-MEMORIAL VOLUME
DISCOURSE

STEREOLOGY: HISTORICAL NOTES AND RECENT EVOLUTION

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ABSTRACT

In the first part of this paper a recent discovery is reported of an early use of the term 'STEREOLOGIE', completely different from the current one. The rest of the paper constitutes an informal account on the recent evolution of stereology, notably on the estimation of particle number, mean size and size distributions. Perhaps the main conclusion reached in this paper takes the form of a good advice given by the late Hans Elias in his After-Dinner talk at the Second International Congress for Stereology (Elias, 1967): "It is up to us stereologists to keep our eyes and ears open ..."

Keywords: disector, number, particles, selector, size distributions, unfolding.

INTRODUCTION

This paper constitutes an informal account of some historical notes on the one hand, and of personal reflections and viewpoints on the state-of-the-art in the stereology of particles on the other.

The main historical note (next section) might convey some perplexity, even a bit of disillusion - mild, I hope! - to many stereologists. I tend to imagine, however, that Hans Elias himself would have seen the note with more excitement and curiosity than disappointment. In order to illustrate the sportsmanlike attitude of H. Elias, let me quote the following paragraph from his Introductory Remarks to the First International Congress for Stereology, in which he refers to another Honorary Member, also Founder of the ISS, who, alas, also left us recently:

> "One day an anatomical mathematician from Munich asked me in a very polite letter whether I would resent if he published a correction to one of my papers which dealt with the percentage-wise distribution of axial

ratios of ellipses, that resulted from cutting randomly distributed cylinders. This man was August Hennig which I should properly call the father of our society. I was not only surprised that there should be another person who played with the geometry of sectioning, but I was glad to have found a man who had a deeper understanding of this field than I. And it came about that August Hennig and I became very close co-workers."

(Elias, 1963)

Thus, after some hesitation I decided to include the following note in this article.

ARE WE SURE WE ARE DOING "STEREOLOGIE"?

A few lines below the paragraph pin-pointed above, Hans Elias wrote the following:

"... I believed that people who do such things should get together. And I announced an informal conference on spatial interpretation of sections on the Feldberg two years ago. At that conference this society was established and, with the aid of a Greek pocket dictionary, we coined the word Stereology after we had convinced ourselves by telephone calls to the Freiburg University library that this word had not yet been used before."

(Elias, 1963)

If at all needed (which I do not imagine) the sentence I have underlined above would be exonerative enough for H. Elias!

My attention has recently been called to an amazing discovery made by the East German mathematician Dietrich Stoyan, from Bergakademie Freiberg, sometime last year. It transpires that, among some items obtained by inheritance, Dr. Stoyan came across a copy of a German 'Handbook of Foreign Words' (a sort of dictionary of words adapted from languages other than German, of technical terms, etc.), compiled by Friedrich Erdmann Petri and published in Gera (now DDR). Apparently, Stoyan's copy was published in 1899. Last June, I made separate enquiries at the DeutschesSeminar of the University of Berne, and I was shown a copy of Petri's dictionary dated 1897 - see Fig. 1a. Yet, the book I borrowed was the 20th reprinting of the 13th edition! I know that the 2nd reprinting of the 13th edition was published in 1889 but, for the time being, I have not searched yet the publication date of the 1st edition.

At any rate, Dr. Stoyan must have been fairly surprised, as I was, when looking into p. 836, the relevant fragment of which is reproduced in Fig. 1b. The term STEREOLOGIE is defined there as:

"Science of crosses, interpretation of all kinds of crosses on coins, emblems and documents."

(Petri, 1897)

Dr. Friedrich Erdmann Petri's

Handbuch der Fremdwörter

in der

deutschen Schrift- und Umgangssprache.

Mit einem

eingefügten Namendeuter und Verzeichniß der fremdsprachigen Wortkürzungen.

20. Stereotypauflage

der dreizehnten neu bearbeiteten und vielfältig vermehrten Auflage

von

Dr. Emanuel Samostz.

Gera,

C. B. Griesbach's Verlag.

1897.

(a)

Stereographīe, f., gr., die Körperzeichnung; stereographisch, körperzeichnend; stereographische Projectiōn, f., der Durchschnittspunkt eines Hauptkreises der Kugel mit der Verbindungslinie des einen Poles und eines Punktes der entgegengesetzten Kugeloberfläche.

Stereologīe, f., Kreuzlehre, Erklärung aller Arten von Kreuzen auf Münzen, in Wappen und Urkunden. [Urstoffen.

Stereomantīe, f., gr., die Wahrsagung aus

Stereomēter, m., gr., ein von Leslie verbessertes, auf dem Gesetze Mariotte's beruhendes Werkzeug zur Bestimmung des Raumes, den poröse oder pulverige Körper einnehmen; Stereometrie, f., die Körpermessung oder Körpermeßkunst; stereomētrisch, körpermessend oder körpermäßig.

Stereoprospettiva, f., gr.-it., erhabne Malerei (mit Auftragung dicker, schattenwerfender Farbenschichten.)

Stereoptīn, n., gr., Aniskampher.

Stereoskōp, n., gr., eine optische Vorrichtung, wodurch man einen in zwei Bildern dargestellten Gegenstand vollkommen plastisch hervortretend erblickt; Stereoskopie, f., die Betrachtung oder Ansicht von Gegenständen in Bildern im Stereoskop.

sterēotisch, gr., dürr, ausgedörrt, durch Ausdörrung entstanden.

Stereotomie, f., gr., die Körpertrennung, Lehre von dem Durchschnitt fester Körper, Steinschnittlehre.

(b)

Figure 1. Reproductions from the 20th printing of the 13th edition of Petri's dictionary, (1897). (a): title page. (b): a fragment of p.836. Note that the second entry reads "Stereologie".

Thus, it seems that "Stereologie" was the name of a discipline dealing with the interpretation (e.g. of authenticity, of provenance, etc.) of seals, motifs or identification marks stamped on coins, messages, official documents and items of diverse kinds. As such, it is therefore not unlikely that the 'art' itself already existed back in the Middle Ages, when a certain symbology played an important role in everyday life (the iconography and architecture of the time, for instance, abound in such meaningful symbols, many of which resist interpretation nowadays).

Curiously, the term "Stereotomie", visible also in Fig.1b, has more to do with what we understand today by stereology than the actual term "Stereologie"! After all, "Stereotomie" dealt with "sections through solid bodies"...

Much later (as far as 1932) William R. Thompson, from the Department of Pathology (Yale University), proposed the term "Projectometry" for what we currently conceive as stereology- but we shall come back with W.R.Thompson in a moment.

Independently of the foregoing notes, I personally feel that the actual choice of the name of our discipline was nice and well chosen. I only come to wonder what will people understand by "Stereology" in one or two hundred years, however!

COUNTING AND SIZING PARTICLES: 'STATE OF THE ART' AND APOLOGIES

Particle number

The concept of 'number' is very primitive indeed: children start counting objects fairly early. It is not surprising, therefore, that the first 'stereological' question made by many people about cells, granules, or whatever particles they want to look at tends to be "how many" are there.

Confronted with the limitation of having to observe cell transects instead of the cells themselves, however, the stereologist traditionally resorted to 'indirect' methods (commonly known as 'unfolding methods') in order to estimate cell size and number in three dimensions from two-dimensional measurements. By now, terms such as "Wicksell", "tomato salad" or "Swiss cheese" problems will be familiar to many readers (if only as responsible for some headaches!).

The main assumptions underlying unfolding methods concern particle shape and, in more 'state of the art' methods, a precise modelling of the distorting effects of section thickness, notably overprojection (traditionally known as 'Holmes effect') and truncation (i.e., loss or unobservability of grazing particle transects). For all this machinery to work, however, the particles must unfortunately be spheres (with very limited concessions, e.g. perfect disks or perfect and parallel solids of revolution). Unfolding methods must therefore yield biased results in general, if only because the underlying assumptions never hold exactly in practice.

Even if the relevant assumptions held 'reasonably approximately' in practice, two serious snags remain. Firstly, and from a strictly mathematical viewpoint, the unfolding problem is known to be numerically 'ill-posed'. The problem has attracted (and is still attracting) the interest of many mathematicians for more than sixty years. The sixty-odd references listed in Cruz-Orive (1983), for instance, represent the best tries among very many and yet, no satisfactory, mathematically stable solution has ever been found which will work in all cases. The second snag is one of efficiency: in the best of the cases the investment in time and effort required to reach a moderate stability in the solution will be too high.

We knew all the above for years - hence, the best recommendation we could give to practical stereologists was: "look again at your problem, and try to re-define the required answer so that you do not need to count!" Yet, of course, counting the things, (or, still worse, knowing their size distribution precisely) would be absolutely essential to many people - hence I felt encouraged myself to enlarge the already long list of 'unfolders' yet again by writing the 1983 paper.

Perhaps the heart of the matter lies in the fact that the mathematical problem is ill-posed just because the physical one is unnaturally posed. For countless years, embedded particles of all sorts have been silently begging to be counted in <u>the</u>

natural manner! The publication of the 'disector' method (Sterio, 1984) has placed us again in a position we should have occupied for many years (at least since 1932, as we shall see). Thus, with rare exceptions we are now glad to hear our clients saying that they want to count things!

In May 1985, on the occasion of the Course in Morphometry and Stereology in Neurosciences held in Amsterdam, Hans Jørgen Gundersen showed in a slide the first page of the paper by W.R. Thompson mentioned in the preceding section (Thompson, 1932). As reported by Gundersen (1986, section 7) this short paper of Thompson describes in a precise, lucid way the following concepts: (i) The associated point rule for assigning a particle to an arbitrary portion of space, as a prerequisite for establishing any direct unbiased counting rule (Miles,1978); (ii) the 'serial stack' method published also 48 years later (Cruz-Orive, 1980) for estimating particle number, and (iii) the essentials of the disector device, re-discovered and improved by Sterio (1984).

As soon as I saw the mentioned slide, I was almost sure I had seen that paper before. On returning to Berne, I soon found the photocopies of both Thompson (1932) and Thompson el al (1932), carefully stapled since my Sheffield years (maybe around 1975) and deposited in a pool of papers deemed of 'lesser importance'. In fact, at the time I came across Thompson's papers I was more interested in the 'exciting' mathematical challenge offered by unfolding-like stereological problems than in solving the real problem of counting. I vaguely remember having set the first paper aside as soon as I discovered that Thompson was resorting to serial sections - this looked like cheating to me! Subconsciously, I was probably convinced that no 'faithful stereologist' should ever use three-dimensional probes!? I do not think, however, that I can blame the 'official' definition of stereology for this. Indeed, I should have been reminded at the time of a closing remark made by H. Elias in one of his papers:

> "It is up to us stereologists to keep our eyes and ears open to reports on inexplicable phenomena. Maybe we shall be able to help our colleagues in other disciplines through our training in extrapolation."
> (Elias, 1967)

At any rate, people could have started counting embedded particles properly as early as 1933 and, out of the 52 years "lost", I tend to feel a bit responsible for the last ten or so.

Quite a similar thing has happened to me regarding the 'fractionator', recently described by Gundersen (1986). A few weeks ago, while looking for a paper by Eva Jensen, I lazily browsed at another reprint lying in the same folder, namely Jolly (1979). The author - whom I know since 1970 - sent this reprint to me shortly after we met again at a statisticians' meeting in Brighton, 1980. In the mentioned reprint, the fractionator principle (in all its generality) and some statistical properties of it, are precisely described. Here it was actually a 'colleague in other discipline' (statistical ecology, as a matter of fact) who was instead offering his help to the stereologist, but the latter did unfortunately not keep his 'eyes and ears' open enough once again!

Mean particle size

It is by now fairly clear that we can estimate the number of arbitrary particles in an embedding medium relatively easily (at any rate with practically no 'algebra' at all), very efficiently and unbiasedly, irrespective of particle shape and orientation, overprojection and truncation - anyone who has faced unfolding problems before knows the value of the preceding statements.

An unbiased estimate of particle number, however, does in general not guarantee the unbiased estimation of mean individual particle volume or surface area, for instance. In fact, the estimates of the numerators of the relevant relationships $\bar{v}_N = V_V/N_V$ and $\bar{s}_N = S_V/N_V$ from a section are unfortunately not free from the bias caused by our old enemies, namely overprojection and truncation. The same remark applies, to various degrees, to the long list of size estimators now available (see for instance Gundersen, 1986, Table 1). In passing, one cannot avoid mentioning the 'mean particle volume-weighted volume' $\bar{v}_V$, which enjoys the distinct privilege of being estimable directly on independent sections without resorting to the knowledge of N_V. The relevant measurements are 'point-sampled intercepts' (Gundersen and Jensen, 1985, see also Cruz-Orive and Hunziker, 1986, Fig. 10). Most point-sampled intercepts actually tend to fall near the equatorial part of the particles, so that the estimate of $\bar{v}_V$ is one of the mean particle size estimates least affected by overprojection and truncation artifacts.

Having removed the bias inherent in any shape assumptions, the impact of the aforementioned bias upon mean particle size estimates should be of lesser importance in most cases, however, and it can often be reduced almost arbitrarily by a careful control of observation conditions, notably by reducing section thickness. Trouble arises, however, when the size of the particles of interest does not extend beyond a few nanometers. Unfortunately, the First Rule of the Game reads, more or less, as follows:

"What we cannot see, we cannot measure".

Mathematical corrections for overprojection effects at least have nevertheless been used for many years (classical, early references are Cahn, 1959, and Cahn and Nutting, 1959; for details and more references see for instance Weibel, 1980, Chapter 4). The ultimate effectiveness of such corrections as 'bias removers' rests again on the assumption of a simple and fixed particle shape, however. This means that the correction problem is essentially equivalent to the unfolding problem, and hence there does not seem to be much scope for further progress in this direction either.

In the stereological literature, it has nearly always been given for granted that any bias corrections for section thickness effects should be corrections for overprojection. That is, traditionally the particles have been assumed to be opaque or, at least, 'more opaque' than the embedding medium. In particular, the correction procedures described in Weibel (1980), in Cruz-Orive (1983),and in practically all the references therein, assume overprojection.

I have tried the aforementioned procedures quite a number of times in order to unfold diameter distributions of hepatocyte nuclei, for instance. One of my colleagues, Dr. Otfried Müller, was concerned about the fact that the algorithms in Cruz-Orive (1983) consistently yielded mean nuclear size estimates which were "too small" in his experience. More recently, O. Müller and I have tried the newer counting techniques on serially cut blocks of rat liver observed by light microscopy. While N_V estimates agree rather closely among different methods, our attempts at estimating say mean nuclear heights (using an unbiased estimate of N_V into an overprojection formula) led to openly contradictory results - that is, the estimated heights were 'too short'. This applied not only to hepatocyte, but to non-hepatocyte nuclei as well.

I experienced a similar problem with Didima de Groot (from NL-Rijswijk) when analyzing E-PTA stained synapses of rat hippocampus from ultrathin serial sections - (for a discussion of the problems inherent in the process of counting and sizing synapses see De Groot and Bierman, 1986). In spite of the fact that synaptic contacts appear as 'black' and the matrix as 'white', we have certainly begun to wonder whether being 'white' implies being 'translucent'!

Thus, evidence is now accumulating in favour of the hypothesis that, in many cases, an underprojection model should be more adequate than an overprojection model. The distinction is important, because a particle height estimate obtained via the underprojection model exceeds the estimate obtained via the overprojection model by two section thicknesses! (provided, of course, that a same, unbiased estimate of N_V is used in both cases - see Cruz-Orive and Hunziker, 1986, equs. (8.1a), (8.1b)).

Quite recently, Ewald R. Weibel has offered me the opportunity to see some of his correspondence (as Past President of the ISS) with Hans Elias. In a letter dated October 1, 1969, the latter writes:

> "The Holmes effect deals with overlap of completely opaque objects. It does not apply to translucent things, such as nuclei in liver cells or oblique membranes.
>
> In liver cells, it does apply to ribosomes and to glycogen particles."

Once again, I should have known that before!

The only treatment I know on the translucent spheres underprojection problem which is general enough is that of

Coleman (1983). A ready-to-use algorithm for unfolding size distributions of translucent spheres based on Coleman's results does not seem to have been published, however.

Although there is certainly a case for seriously considering the underprojection effect, at least in biology, the 'truth' is, as usual, likely to lie in the middle: we will seldom have either pure overprojection or pure underprojection. The physical artifacts introduced by section thickness are probably too complex to admit simple corrections which are useful and realistic in every particular case.

Particle size distributions

As we have mentioned, particle number can be unbiasedly estimated by any direct counting method. Presently - September 1986 - the list of direct unbiased probes reads: the serial stack, the disector, the unbiased brick, the fractionator and the selector. For details see for instance Gundersen (1986) or Cruz-Orive (1986). As we have also seen, having N_V means having ordinary (i.e. number-weighted) mean particle sizes, e.g. $\bar{v}_N = V_V/N_V$, $\bar{s}_N = S_V/N_V$ and $\bar{h}_N = N_A/N_V$, (albeit somewhat biased by section thickness and truncation artifacts, as already discussed). Moreover, the mean particle volume-weighted volume $\bar{v}_V$ is directly available on independent random sections via point-sampled intercepts, whereby also the coefficient of variation of particle volumes, namely $CV_N(v) = SD_N(v)/\bar{v}_N$, is estimable without actually knowing the particle size distribution at all. This is easily achieved using the identity $CV_N(v)=(\bar{v}_V/\bar{v}_N - 1)^{1/2}$, (to see this, note that $\bar{v}_V$ is just $\overline{v_N^2}/\bar{v}_N$ and that $Var_N(v) = \overline{v_N^2} - (\bar{v}_N)^2$).

The foregoing remarks mean that particle number, mean sizes and variation in size are available without having to estimate any particle size histograms. In order to please the more exigent customer who also wants the actual size distribution (e.g. in order to study nuclear ploidies), the only unbiased way we know at present to estimate such distributions for a population of embedded particles essentially consists of the following two steps:

(i) Sample a number of particles with identical probabilities using disectors of technically well chosen but otherwise unknown thickness(i.e. selectors).

(ii) For each of the particles sampled in the preceding step, measure the required size parameters as accurately as possible - this will normally necessitate the use of ancillary serial sections through the sampled particles.

The collection of particle sizes so obtained will estimate the required size distribution unbiasedly without further qualification - see for instance Gundersen (1986, section 3.3), Braendgaard and Gundersen (1986, section 1.3) and Cruz-Orive(1986).

The main problem encountered in the preceding method, however, is how to measure a particle size parameter accurately from serial sections of the particle. This is discussed next.

To start with, if a particle is close to a sphere or to a circular disk in shape, then the diameter of the biggest profile in the series of ancillary sections through the particle will be close to the true diameter of the particle.

For an arbitrary particle sampled as indicated in step (i) above, we shall consider only the estimation of its volume and surface area.

In order to get rid of the bad news first, it must be said that no reasonably accurate estimate of surface area exists for an arbitrary particle from a set of parallel serial sections of it (see also Gundersen, 1986, p.30). If the particle could be handled at will, like a (cold!) potato or a clay figurine of a Paddington bear, then the situation would be quite different (see Baddeley et al., 1986, Fig.9), but here we are unfortunately talking about small particles embedded in situ. This leaves us with the hope of getting the volume distribution at least...

If the distance between say the upper faces of the sections used for analysis is not known, then we can still get an unbiased estimator of the volume of the particle by measuring point-sampled intercepts on these sections. The volume estimate so obtained can yield an accurate estimate of mean particle volume $\bar{v}_N$ when combined with the analogous estimate obtained for say another 40 or 50 different particles (sampled with identical probabilities all of them) but, unfortunately, it is not accurate enough to be used individually. In other words, a histogram made with such volume estimates will in general be quite different from the true volume distribution.

As a handy interlude, the positive feature of the preceding approach is that, having access to an accurate estimate of $\bar{v}_N$ (namely the mean volume of all particles) enables us to estimate particle number indirectly via the identity $N_V = V_V/\bar{v}_N$. And the remarkable fact is that section thickness is used nowhere: this is the essence of the selector method for estimating particle number (Cruz-Orive, 1986).

Coming back to the volume distribution problem, an unbiased and precise estimator of the volume of each individual particle in the sample can be obtained using Cavalieri's approach, namely as a product of total transect area in the serial sections through the particle times the mean distance between the upper faces of the sections (which reduces to mean section thickness if the sections are adjacent). For further refinements, notably for removing some of the bias caused by either over- or under-projection, see Gundersen (1986, equ. (4.1)).

In short, the main technical requirement for obtaining an unbiased estimate of particle volume distribution is a reliable assessment of section thickness.

A final note on B. Cavalieri

There is perhaps a certain parallelism between the approach adopted by the Italian mathematician Bonaventura Cavalieri (1598 - 1647) in his famous "Geometria degli Indivisibili" (Cavalieri, 1635, 1966 - see Fig. 2 below) and the current evolution of stereology.

(a) (b)

Figure 2. (a): Buonaventura Cavalieri and (b): reproduction of the title page of his Geometria degli Indivisibili published in 1635.

Indeed, up to Cavalieri's time the prevailing mathematics (and science at large, notably astronomy) were dominated by the traditional Greek geometry, the central object of which was the exhaustive study of the properties of regular (e.g. 'Platonic') solids. Archimedes, for instance, excelled in the development of beautiful geometry for such model solids, notably using his celebrated limiting procedures in order to find the exact areas and volumes of many such solids, (see e.g. Heath, 1960). In a quite different fashion, however, Cavalieri simply ignores any assumptions regarding shape, and he establishes instead a general definition of volume for an arbitrary solid by way of comparison of its lower-dimensional sections with those of a reference solid of the same 'height'. He thereby implicitly expresses a volume as a sum of section areas (up to a constant which is of course the mean distance between the sections). This was also the 'method of Archimedes', but the latter incorporates shape assumptions, however, in order to proceed further via limiting procedures. Thus, Cavalieri sacrifices the explicit, model-based result in favour of a more general (in modern terms 'non-parametric') approach.

As a very minor tribute, it seems therefore fair that the unbiased estimator of the volume of an arbitrary solid from parallel systematic sections is named after Cavalieri, as already suggested in Sterio (1984, p.131).

CONCLUSIONS AND COMMENTS

The recent discovery of an earlier use of the term 'Stereologie' - quite different from the current one - by D.Stoyan, again illustrates how difficult is to coin anything entirely 'new'. This particularly applies as well to the 'modern' unbiased counting probes, some of which were anticipated by W.R. Thompson in 1932. In turn, it is not unlikely that the latter was simply collecting a number of ideas which were already 'in the air' at the time.

The anecdotes about Thompson's paper, for instance, should constitute a warning against our discarding a paper or an idea before adopting certain precautions - i.e. "to keep our eyes and ears open", in H.Elias' words.

On the more technical side, an important conclusion is that, with the advent of the direct, unbiased sampling probes, the practical stereology of particles is likely to be deeply affected, and the era of 'unfolding methods' might thereby be well over.

The methods discussed in this paper pertain mainly to what could be called 'classical stereology', namely methods for estimating global quantities such as volume, surface area and number of particles. The evolution here has been fast during the last two or three years, and it clearly points toward freedom from shape assumptions. Notable developments here are the vertical sections design, the point-sampled intercept methods, and the various unbiased counting procedures. The number of theoretical and practical barriers has therefore been significantly reduced in classical stereology and, although there will always remain a substantial scope for theoretical work in the classical domain, it is clear that new problems and new questions have to be addressed from now on. These problems concern for instance the quantitative characterization of spatial relationships (including questions about 'pattern', 'shape', etc.) of which very little is as yet understood. A realistic approach to these problems transcends the use of traditional analytical methods, however. In the statistical analysis of spatial point processes, for instance, classical hypothesis testing often has to be replaced with so-called Monte Carlo hypothesis testing, based upon data-based computer simulations (see e.g. Diggle, 1983). More generally, the properties of random sets, their modelling, characterization and analysis are as yet far from well understood - only the special

'Boolean model' based upon the Poisson point process is relatively easy to handle, but this is unfortunately unrealistic in most cases, however. The available literature does not cover far beyond general formulations for the foundation of a mathematical theory. Still more than in the case of point processes, further progress in the modelling and concrete analysis of realistic random sets seems hardly possible without the intelligent use of an open, research-oriented image analyzing device.

In short, a new brand of problems are already 'calling to our door' to mark the start of a new era in stereology.

ACKNOWLEDGEMENTS

I wish to thank Marianne Schweizer for making the pictures. Work supported by the Swiss National Science Foundation grant No. 3.524.83.

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