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Mitochondria Stereology From the Statistics of Sections

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The motivation for this research comes from the study of conformational changes in mitochondria associated with cell death. During late stages of apoptosis (programmed cell death) the cell's mitochondrial network fragments from long tubules into individual mitochondria. Such fragmentation is due to the suppression of the fusion process, which is enacted during apoptosis. Cross-sections of these particles observed in electron micrographs suggest that they have an oblong shape resembling a prolate spheroid. These mitochondria are believed to undergo changes over time in shape and size due to disruption of inner membrane function and possible resultant swelling. While confocal light microscopy is able to partially document this process, the resolution is limited to values comparable to the particle size. The only accurate quantitative information on size and shape is obtained from electron micrographs. However, these micrographs are of 2-dimensional cross-sections of the particles; direct 3-dimensional information on size and shape is lost in this process. Nevertheless, if we assume the mitochondria take a simple enough form, e.g. prolate spheroid, it is possible to infer 3-dimensional information from the statistics of the 2-dimensional sections. It is this stereological problem that we propose to address.

The basic mathematical problem is to relate the distributions of observable quantities in 2D cross-sections to the distributions of desired quantities that are descriptive of the 3D particles. Typically this takes the form of an integral transform expressing, for example, the distribution Ψ of cross-sectional diameters in terms of the distribution Φ of particle diameters. The practical problem is then to use this machinery to work from data in the form of a sample of Ψ to a description of Φ. Some methods for solving this problem were identified by S. D. Wicksell in 1925[i]. For example, the integral transform can then be used to derive a recursive scheme that expresses the moments of Φ in terms of those of Ψ. Also, it is sometimes possible to invert analytically the transform and to solve for Φ in terms of Ψ and its derivatives. Both of these approaches suffer when the data set is not large enough to provide a clear picture of Ψ. Furthermore, in the first approach, statistical moments from the data are only estimates of Ψ's true moments. Similarly, in the second approach, estimates of the derivatives of Ψ by finite difference methods introduce uncertainties that are difficult to quantify. We offer a new approach, which does not seem to have been used by previous authors in the context of the corpuscle problem. We propose parametric models for desired distributions similar to the parameters. This method has the advantage of simplicity in the implementation as well as in the handling of uncertainties; the likelihood ratio test can be used to set confidence intervals for the parameters.

Our method involves many steps. First we set out a geometrical framework and define the quantities studied, both measured and desired, and state the relations among them. Next, we apply the method of Sato to derive the machinery expressing the measured distributions of cross-sectional size and shape to the hypothetical or desired distributions of particle size, shape, and orientation[ii]. We then describe the parametric models used for the hypothetical distributions and the maximum-likelihood scheme used to determine values for the parameters. Finally, we applied our method to a sample of 231 traces of mitochondria from electron micrographs of HeLa cells.

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[i] S. D. Wicksell, The corpuscle problem. A mathematical study of a biometric problem. Biometrika, 17, 84 (1925)

[ii] Eiichi Sato, Naoki Kondo and Fumihiro Wakai, Particle size, shape and orientation distributions: general spheroid problem and application to deformed Si_3N_4 microstructures. Philosophical Magazine A, 74(1), 215 (1996).