Theoretical ellipsoidal model of gastric electrical control activity propagation

Andrei Irimia and L. Alan Bradshaw
Living State Physics Laboratories, Department of Physics and Astronomy, Vanderbilt University, Nashville, Tennessee 37235-1807, USA
(Received 23 May 2003; published 20 November 2003)

A theoretical model of electric current propagation in the human stomach is developed using an approach in which the shape of the organ is assumed to be a truncated ellipsoid whose dimensions can be determined from anatomic measurements. The gastric electrical activity is simulated using a ring of isopotential electric current dipoles that are generated by a pacemaker situated in the gastric corpus. The dipoles propagate in the direction of the pylorus at a frequency of three cycles per minute. The advantages of employing ellipsoids in the analytical formulation of this gastric model are discussed in addition to the realism and usefulness of the approach.

DOI: 10.1103/PhysRevE.68.051905 PACS number(s): 87.19.Nn, 87.17.Aa, 87.10.+e

I. INTRODUCTION

The study of the electrical control activity (ECA) associated with the stomach is of great interest in medical biophysics due to the numerous investigations that have been carried out to detect abnormal conditions of this organ in various ways, particularly using electrogastrograms (EGG) or magnetogastrograms [1–6]. The ECA in the stomach is generated due to the periodic depolarization and repolarization of cells located in the body of this organ and originates in the corpus as a wave propagating aborally towards the pylorus through the electrical syncytium of the stomach.

Throughout a typical propagation cycle, the amplitude of the electric potential recorded from a healthy human subject increases by more than one order of magnitude, while the propagation velocity is thought by some researchers [7] to reach around 4 $\mathrm{cm\,s^{-1}}$ in the pylorus from the approximate value of 0.3 $\mathrm{cm\,s^{-1}}$ at the beginning of a cycle. Lately, consistent efforts in the direction of modeling the complex phenomenon of gastric electrical activity have led to the development of various analytical and numerical electric wave propagation models that can reproduce EGG recordings [8–10,7].

II. MOTIVATION AND PURPOSE

The purpose of this paper is to propose an ellipsoidal model of gastroelectrical activity based on known anatomical and physiological characteristics of the gastrointestinal (GI) tract and to predict some of its possible advantages. In comparison with cones or cylinders, which have already been used for modeling the stomach [7,11,12], ellipsoids may account in a more natural way for the rate in which the diameter of the GI tract diminishes in the region of the pylorus. This may indicate that ellipsoids are potentially useful for simulating the electric coupling of current sources in the stomach.

By using ellipsoids truncated along the plane in which the gastric activity originates, it can be of interest to model gastric electrical currents by taking into account the behavior of electric field phase velocities as functions of time. Moreover, determining the electric potential outside the stomach using our model may be convenient for investigating the magnetic fields that are associated with it [13–15]. This possible application may be relevant in studies that involve noninvasive methods of diagnosis, where the electric potential and the magnetic fields in the stomach are of interest and can be detected noninvasively using, for example, superconducting quantum interference device magnetometers.

In a previous model of gastric electrical current propagation [16–18], the magnetic field at the surface of the stomach due to current dipoles on a propagating annular ring was approximated by a single dipole located at the center of the ring. This single-dipole model was used successfully for studying the gastric electrical activity (GEA) from noninvasive measurements of electric potentials, but was found to be rather inadequate for modeling this phenomenon at a more detailed level. Some of the other models that have appeared in the literature [7], although quite realistic, are not always as successful in simulating the characteristics of this phenomenon as some of the more intensely computational methods that have been proposed [8,11,12]. On the other hand, it is useful to note the fact that in addition to being less straightforward to implement and understand, complex computational models may not always lead to the simplest realistic estimations of gastric electric fields. This may be a possible disadvantage in studies that do involve the use of GEA modeling but which are not systematically concerned with all the details of the model itself. In light of these alternatives, it is useful to note that our method is not as intensely computational as some of the others that have been developed [11,12]; however, we believe that it has the advantage of being sufficiently simple, comprehensive, and precise to model the GEA accurately enough for the purposes of many applications without overlooking the overall complexity of the phenomenon being modeled.

III. THEORETICAL MODEL

As it has been already proposed in other studies of bioelectric current propagation [7,11,12,19], the gastric electrical activity can be modeled by an annular band polarized by electric current dipoles [20] that move across the body of the stomach from the corpus in the direction of the pylorus [21]. In agreement with other common models of propagation and with the phenomenology of the GI tract [11,22], the current dipoles on this annular band can be considered to be perpendicular to the surface of the gastric wall and oriented either inward [7] or along the direction of propagation [43]. In humans, a typical GEA cycle begins roughly two thirds of the way along the greater curvature of the stomach and propagates towards the pylorus with increasing velocity [11,12]. Since the electrical activity above the gastric pacemaker is negligible from the perspective of propagation [11,12], one can assume that it is sufficient to take into account for the purposes of this theoretical model only the truncated section of the ellipsoid positioned immediately below that region.

In some applications, ellipsoids may be preferable to cones for modeling the GEA due to the agreement of the former with the anatomic configuration of the stomach, particularly in the regions of the pylorus and of the corpus, about half of the way along the greater curvature of the organ. These objects have a simple geometry and mathematical formulation, and for certain studies they may represent viable alternatives to truncated conoids and to other geometrical shapes [22–25], some of which are associated with more elaborate numerical approximations of the electric potential. Although our mathematical model does require numerical integration, the approach that it proposes is simple and easy to implement in comparison with a number of other models of electrical activity that have been published.

In the quasistatic approximation, the electrical current dipoles that propagate through the stomach wall can be modeled using a circular band of width ΔR which moves along the body of an ellipsoid with constant acceleration. As predicted by electromagnetic field theory [7], the electric potential V of an electric current dipole in a homogeneous medium due to a current dipole in this wall is given by the equation

$$V(\mathbf{r})=\frac{1}{4\pi\epsilon_0}\frac{\mathbf{p}\cdot(\mathbf{r}-\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^3}, \tag{1}$$

where the vector $(\mathbf{r}-\mathbf{r}')$ points from the source of the potential $\mathbf{r}'$ to the measurement point $\mathbf{r}$ and ϵ_0 is the permittivity of free space. For an isopotential band of dipoles, the total potential at any point in space becomes the sum of potentials due to each of the n dipoles on the annular band, in which case the substitution $\mathbf{p}\equiv\boldsymbol{\rho}dS$ can be made, where $\boldsymbol{\rho}$ is a vector denoting the dipole density of the propagating band. By using the limit of a Riemann sum to define the surface, the potential due to the propagating current dipoles is then given [27] by the formulas

$$V(\mathbf{r})=\frac{1}{4\pi\epsilon_0}\lim_{||\Delta||\to 0}\sum_{i=1}^{n}\sum_{j=1}^{m}\frac{\boldsymbol{\rho}\cdot(\mathbf{r}-\mathbf{r}'_{ij})}{|\mathbf{r}-\mathbf{r}'_{ij}|^3}\Delta x'_i\Delta z'_j$$
$$=\frac{1}{4\pi\epsilon_0}\int_S\int\frac{\boldsymbol{\rho}\cdot(\mathbf{r}-\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^3}dS, \tag{2}$$

where the dipole moment of the annular band was rewritten in terms of the dipole surface density $\boldsymbol{\rho}$ and of the infinitesimal surface element dS. This iterated integral can be recast [26,28,29] into the standard Cartesian form

$$V(\mathbf{r})=\frac{1}{4\pi\epsilon_0}\int_S\int\frac{\boldsymbol{\rho}\cdot(\mathbf{r}-\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^3}\times\left[\left(\frac{\partial\zeta}{\partial x'}\right)^2+\left(\frac{\partial\zeta}{\partial z'}\right)^2+1\right]^{1/2}dx'dz', \tag{3}$$

where $\zeta(x',z')$ can be obtained by solving for the variable y' in the standard equation of the ellipsoid:

$$\zeta(x',z')=\beta\left(1-\frac{z'^2}{\gamma^2}-\frac{x'^2}{\alpha^2}\right)^{1/2}. \tag{4}$$

From expressing the equation of the ellipsoid in Cartesian coordinates [28], one can define a useful function ξ as

$$\xi(x',y',z')=y'-\zeta \tag{5}$$

such that the gradient of ξ is normal with respect to the level surface through any point (x',y',z') on the ellipsoid. The parameters α, β, and γ can be determined experimentally given that they are the spatial extremities of the spheroid, i.e., stomach, in the $\hat{\mathbf{i}}$, $\hat{\mathbf{j}}$, and $\hat{\mathbf{k}}$ directions, respectively, assuming that the body is located along the y' axis and centered at the origin. To evaluate the dot product $\boldsymbol{\rho}\cdot(\mathbf{r}-\mathbf{r}')$, it is sufficient to recall that $\boldsymbol{\rho}$ is a vector perpendicular to the ellipsoidal propagation surface and that $\boldsymbol{\nabla}'\xi$ is normal with respect to this surface and opposite in direction to $\boldsymbol{\rho}$. Normalization of this vector and multiplication by (-1) yields a unit vector perpendicular to the surface of the ellipsoid and directed inwards. If this resulting vector is then further multiplied by the magnitude of the dipole density vector associated with the surface of the annular band, one can obtain an algebraic expression for the dipole density vector as a function of location on the band:

$$\boldsymbol{\rho}=-p_0\frac{\boldsymbol{\nabla}'\xi}{|\boldsymbol{\nabla}'\xi|}, \tag{6}$$

where $p_0\equiv|\mathbf{p}_0|$, i.e., the magnitude of the dipole density vector, becomes a parameter to the equation that can be determined based on experimental information and $(-\boldsymbol{\nabla}'\xi)|\boldsymbol{\nabla}'\xi|^{-1}$ is the downward unit normal with respect to the surface of the ellipsoid. Due to the anatomical configuration of the stomach, the simplifying assumption can be made that the ellipsoid is a spheroid elongated along the y axis of propagation, i.e., $\alpha=\gamma$ and $\beta>\alpha$. These two restrictions are consistent with the fact that the stomach has an approximately circular cross section. After mathematical manipulation, the dipole density function $\boldsymbol{\rho}$ for the band of dipoles can be found to be

$$\boldsymbol{\rho}(x',y',z')=-p_0[\alpha^4-(\alpha^2-\beta^2)(x'^2+z'^2)]^{-1/2}\times\{\beta(x'\hat{\mathbf{i}}+z'\hat{\mathbf{k}})+\alpha[\alpha^2-(x'^2+z'^2)]^{1/2}\hat{\mathbf{j}}\}. \tag{7}$$

The surface integral that gives the total potential then becomes

$$V(x,y,z) = -p_0 \frac{1}{4\pi\epsilon_0} \int_S \int \frac{1}{|\nabla' \xi|} \frac{(\nabla' \xi)\cdot(\mathbf{r}-\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^3} \times \left[\left(\frac{\partial \zeta}{\partial x'} \right)^2 + \left(\frac{\partial \zeta}{\partial z'} \right)^2 + 1 \right]^{1/2} dx' dz'. \quad (8)$$

Expressing the infinitesimal surface element of an ellipsoid is cumbersome in spherical polar coordinates [30] and it is in fact preferable to continue derivations using the Cartesian form. Since the expression above must involve only two variables, the variable y' in the quantity

$$k(x',y',z',x,y,z) = \frac{\nabla' \xi \cdot (\mathbf{r}-\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^3} \quad (9)$$

must be parametrized in terms of x' and z' such that $y' \equiv \zeta$. This leads to the expression

$$V(\mathbf{r}) = -p_0 \frac{1}{4\pi\epsilon_0} \int_S \int f(x',z',x,y,z) dx' dz', \quad (10)$$

where

$$f(x',z',x,y,z) \equiv g(x',z',x,y,z) h(x',z',x,y,z) \times j(x',z') l(x',z') \quad (11)$$

is a product of functions given by

$$g(x',z',x,y,z) = \beta[x'(x-x') + z'(z-z')] + \alpha(y-\zeta)[\alpha^2 - (x'^2 + z'^2)]^{1/2}, \quad (12)$$

$$h(x',z',x,y,z) = \frac{1}{[(x-x')^2 + (y-\zeta)^2 + (z-z')^2]^{3/2}} = \frac{1}{|\mathbf{r}-\mathbf{r}'|^3}, \quad (13)$$

$$j(x',z') = \frac{1}{\alpha} \left[\frac{\alpha^4 - (x'^2+z'^2)(\alpha^2-\beta^2)}{\alpha^2 - (x'^2+z'^2)} \right]^{1/2}, \quad (14)$$

and

$$l(x',z') = \frac{1}{[\alpha^4 - (\alpha^2-\beta^2)(x'^2+z'^2)]^{1/2}}. \quad (15)$$

At this point conversion to polar coordinates can straightforwardly be made according to the transformations $x' \rightarrow r' \cos\theta'$, $z' \rightarrow r' \sin\theta'$ and $x \rightarrow r \cos\theta \sin\phi$, $y \rightarrow r \sin\theta \sin\phi$, and $z \rightarrow r \cos\theta$. The definite surface integral can thus be conveniently written in the form

$$V(\mathbf{r}) = -\frac{p_0}{4\pi\epsilon_0} \int_0^{2\pi} \int_{R_0}^{R_0+\Delta R} f(r',\theta',r,\theta,\phi) r' dr' d\theta' \quad (16)$$

where the variable ϕ is only necessary for the conversion of $\mathbf{r}$ to spherical polar coordinates since $\mathbf{r}'$ was written in terms of two variables and integration is performed in the $x'-z'$ plane. Analytical integration of this expression is cumbersome; alternatively, a numerical integration technique can be employed.

To model the velocity of the current dipoles as the annular band propagates through the stomach, it is necessary to take into account the fact that the position function must obey the boundary conditions $y'(0\text{ s}) = \lambda(\text{m})$ and $y'(20\text{ s}) = -\beta(\text{m})$ such that one cycle of propagation takes 20 s. The constant λ represents the y'-coordinate position of the gastric pacemaker where each propagation cycle begins. The plane $y' = \lambda$ thus represents the limit of the truncated ellipsoid in the upper portion of the stomach, where the pacemaker is located.

After algebraic manipulation, one can find the expression for the radius of the annular band R as a function of time to be given by

$$R(t) = \alpha^2 \left\{ 1 - \frac{[y'(t)]^2}{\beta^2} \right\}, \quad (17)$$

where $y'(t)$ is the vertical plane of the annular band as it moves in the direction of the pylorus. To compute the electric field outside the ellipsoid, the quantity

$$\mathbf{E} = \frac{p_0}{4\pi\epsilon_0} \nabla \left[\int_0^{2\pi} \int_{R_0}^{R_0+\Delta R} f(r',\theta,r,\theta,\phi) r' dr' d\theta' \right] \quad (18)$$

can be evaluated numerically using a Volterra series expansion. As suggested by an anonymous reviewer, this numerical method has the advantage of including phase information [31–34], which makes it preferable to a second-order, three-dimensional Taylor series, for example. The annular band can be assumed to exhibit positive constant acceleration; fitting the boundary conditions $y'(0\text{ s}) = \lambda(\text{m})$ and $y'(20\text{ s}) = -\beta(\text{m})$, where y' represents the position function of the band, leads to the derivation of the annular band position function

$$y'(t) = 2.375\times 10^{-3} t^2 - 5.5\times 10^{-2} t + 5\times 10^{-2} \quad (\text{m}), \quad (19)$$

which can be used for simulating the time evolution of the electric potential described here.

To validate our model and analyze its implications, a computer simulation of the electric potential predicted by our theory for chosen locations above the stomach was developed. The electric potential and the electric field due to the displacement of the ring across the stomach body were both computed. To evaluate the potential, multiple numerical integration was performed in two dimensions using Simpson's $\frac{1}{3}$ rule for polar coordinates to obtain the potential V. As an example, we present in Fig. 1 the simulated electric potential for a point in the stomach with $(x,y,z) = (0,0,0)$ cm, using the coordinate system of Fig. 2. Our wave form agrees with that obtained by Mirizzi *et al.* [7] using a cone model for the same type of simulation.

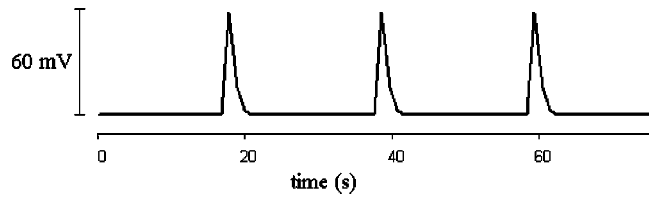

FIG. 1. The electric potential V simulated using the ellipsoidal model for the point $(x,y,z)=(0,0,0)$ cm, i.e., inside the stomach and along the y' axis of propagation.

IV. DISCUSSION

We take note of how various simplified versions of the propagating annular band model used in other studies [16–18] were able to accurately model the GEA. Computationally, the annular band can be approximated in our case by a limited number of dipoles propagating across the surface of the ellipsoid. Ultimately, one can make the assumption that the potential is due to the presence of one dipole located at the center of the propagating ring. This is valid only for points located far enough from the source, which is often not the case in many biomedical studies. In a large number of noninvasive experimental investigations [36], recordings of electric or magnetic fields are made close to the surface of the stomach and the method used for computing the electric potential must subsequently be more accurate than as given by a one-dipole model. It is then not only of theoretical but also practical interest [37] to determine how many current dipoles are necessary to simulate the potential due to the annular band of homogeneous dipole density $\boldsymbol{\rho}$ within a certain accuracy. This is important because it allows one to ascertain the extent to which the present approach is more precise than the simpler model that we developed [16–18] and which simulates the GEA using a single current dipole. The difference in accuracy between the two theoretical estimations can be quantified in the least-squares sense by making use of the formula

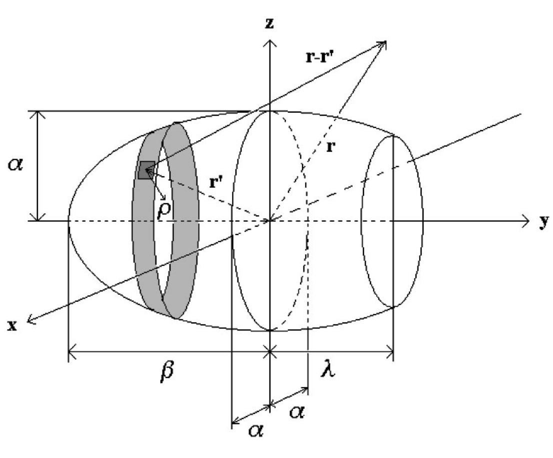

FIG. 2. Visual representation of the ellipsoidal gastric electrical current propagation model. The electric potential V is due to an annular band of dipole density $\boldsymbol{\rho}$ that moves in the direction of the pylorus, i.e., in the direction of the negative y axis in this figure. A GEA cycle begins in a vertical plane perpendicular to the y axis, where the body of the ellipsoid is truncated; this is also the plane that corresponds to the position of the gastric pacemaker.

$$(\Delta V)^2=(V_d-V_e)^2, \tag{20}$$

where V_d and V_e are the potentials predicted by the one-dipole and ellipsoidal (present work) models, respectively. In the second approach, $\mathbf{r}'\equiv\mathbf{y}'\equiv\zeta$ because the center of the annular band moves along the y' axis during each cycle of propagation. The expression above then becomes

$$(\Delta V)^2=\frac{1}{8\pi^2\epsilon_0^2}\left[\frac{\mathbf{p}\cdot(\mathbf{r}-\zeta)}{|\mathbf{r}-\zeta|^3}+p_0\int_0^{2\pi}\int_{R_0}^{R_0+\Delta R}f(r',\theta',r,\theta,\phi)r'dr'd\theta'\right]^2, \tag{21}$$

which can be used to measure the improvement proposed by our model. Although an experimental study that would allow this improvement to be quantified has not been performed yet, a statistical investigation focusing on one dipole for modeling the GEA [35] suggests that a more sophisticated model—such as the one presented here—may indeed be necessary in some simulation studies. It therefore remains to be accurately determined as to what extent one can safely simplify the model of the GEA by using a cylindrical body without omitting important information about this phenomenon from the theoretical formulation.

One possible disadvantage of the approach presented here is the fact that it neglects the inhomogeneities of the abdominal medium. Other GEA models that have been developed [7,11,12,22] also assume Eq. (1) to derive a formula for the electric potential due to a moving polarized band. The assumption of homgeneity greatly simplifies our modeling problem, although an inhomogeneous extension is also possible. Studies that incorporate this aspect have been performed, for example, in cardiac modeling [38]. Our theoretical approach is suitable for adaptation in this respect because, in our model, the electric potential in Eq. (2) is due to a distribution of current dipoles on the surface of an ellipsoid. This mathematical formulation can be used to apply, for example, a piecewise-homogeneous model as proposed by Sarvas and Hämäläinen *et al.* [39–41]. In their procedure, the volume currents $-\sigma\boldsymbol{\nabla}V$ are replaced by secondary currents on the boundaries between the inhomogeneous conductors being considered [42], provided that the conductivities of the latter do not differ greatly. In order to use this piecewise-homogeneous model, the surface integrals for the potential must be evaluated. In our case, however, since Eq. (8) already provides a formulation of this integral for the stomach, the extension of our model to include piecewise-homogeneous conductors follows more clearly. The inclusion of homogeneity can also address another limitation of our model, namely, the assumption that the stomach body is surrounded by a dielectric medium. By modeling the surrounding abdominal organs as piecewise-homogeneous bodies of varying conductivities, this constraint can also be removed.

Although the modifications presented above can all be implemented, the assumption of homogeneity does offer the possibility to study the most important aspects of the GEA in a straightforward manner [16–18,44]. The inclusion of inhomogeneity may therefore not be required in most cases unless this particular modeling aspect is essential to a study. A theoretical investigation that addresses not only the limitations of our present model but also the electrical response activity phenomenon is currently under way.

Modeling gastric electrical activity is important for acquiring a better [44] understanding of the physiological processes in the human stomach. Our ellipsoidal model of the GEA has a number of advantages in this respect, which may prove useful in future attempts to accurately capture and describe the important aspects of this phenomenon.

ACKNOWLEDGMENTS

The authors are grateful for the research funding provided for this undertaking by the National Institute of Health, Grant No. 1RO1 DK 58697 and by the Veterans' Affairs Research Service.

[1] L.A. Bradshaw, W.O. Richards, and J.P. Wikswo, Jr., Med. Biol. Eng. Comput. **39**, 35 (2001).
[2] L.A. Bradshaw, R.S. Wijesinghe, and J.P. Wikswo, Jr., Ann. Biomed. Eng. **29**, 214 (2001).
[3] R.D. Rothstein, A. Alavi, and J.C. Reynolds, Dig. Dis. Sci. **38**, 1518 (1993).
[4] B. Kothapalli, Med. Biol. Eng. Comput. **31**, 482 (1993).
[5] T.Y. El-Sharkawy, K.G. Morgan, and J.H. Szurszewski, J. Physiol. (London) **279**, 291 (1978).
[6] S.K. Sarna, E.E. Daniel, and Y.J. Kingma, Dig. Dis. **17**, 299 (1972).
[7] N. Mirizzi, R. Stella, and U. Scafoglieri, Med. Biol. Eng. Comput. **23**, 33 (1985).
[8] B. Kothapali, IEEE Trans. Biomed. Eng. **39**, 1005 (1992).
[9] M.A. Amaris *et al.*, Dig. Dis. Sci. **47**, 2480 (2002).
[10] D.B. Geselowitz, IEEE Trans. Magn. **6**, 346 (1970).
[11] M.P. Mintchev and K.L. Bowes, Med. Biol. Eng. Comput. **33**, 179 (1995).
[12] M.P. Mintchev and K.L. Bowes, Med. Eng. Phys. **20**, 177 (1998).
[13] J. C. Mosher, R. M. Leahy, and P. S. Lewis, Proceedings of the International Conference on Acoustics, Speech and Signal Processing, 1995 (unpublished), p. 2943.
[14] S. Baillet, J. C. Mosher, and R. M. Leahy (unpublished).
[15] D.B. Geselowitz, Biophys. J. **7**, 1 (1967).
[16] A. Irimia and L. A. Bradshaw, Proceedings of the IASTED International Conference on Applied Modeling and Simulation, 2002 (unpublished), pp. 56–60.
[17] A. Irimia and L. A. Bradshaw, Proceedings of the IASTED International Conference on Applied Modeling and Simulation, 2002 (unpublished), pp. 51–55.
[18] A. Irimia, Proceedings of the IASTED International Conference on Applied Modeling and Simulation, 2002 (unpublished), pp. 45–50.
[19] N. Mirizzi, R. Stella, and U. Scafoglieri, Med. Biol. Eng. Comput. **24**, 157 (1986).
[20] A.J.P. Smout, E.J. Van der Schee, L.M.A. Akkermans, and J.L. Grashuis, Scand. J. Gastroenterol. Suppl. **96**, 11 (1984).
[21] B.O. Familoni, T.L. Abell, and K.L. Bowes, IEEE Trans. Biomed. Eng. **42**, 647 (1995).
[22] M.P. Mintchev *et al.*, IEEE Trans. Biomed. Eng. **44**, 1288 (1997).
[23] P.Z. Rashev, M.P. Mintchev, and K.L. Bowes, IEEE Trans. Inf. Technol. Biomed. **4**, 247 (2000).
[24] M.P. Mintchev, A. Girard, and K.L. Bowes, IEEE Trans. Biomed. Eng. **47**, 239 (2000).
[25] M.P. Mintchev and K.L. Bowes, Med. Biol. Eng. Comput. **36**, 95 (1998).
[26] J. Stewart, *Calculus: Early Vectors* (Brooks/Cole, Pacific Grove, 1998).
[27] E. W. Swokowski, M. Olinick, and D. Pence, *Calculus*, 6th ed. (Prindle, Weber & Schmidt, Boston, 1994).
[28] R. E. Larson, R. P. Hostetler, and B. H. Richards, *Calculus with Analytic Geometry* (Heath, Lexington, 1994).
[29] G. B. Folland, *Real Analysis: Modern Techniques and Their Applications* (Wiley, New York, 1984).
[30] See http://www.mathcurve.com/surfaces/ellipsoid/ellipsoid.shtml
[31] V. Volterra, *Theory of Functionals and of Integral and Integro-differential Equations* (Blackie, London, 1931).
[32] M. Schetzen, *The Volterra and Wiener Theories of Nonlinear Systems* (Wiley, New York, 1980).
[33] P. Wambacq and W. Sansen, *Distortion Analysis of Analog Integrated Circuits* (Kluwer Academic Publishers, Boston, 1998).
[34] J. Vuolevi, Ph.D. dissertation, University of Oulu, 2001 (unpublished).
[35] A. Irimia and L. A. Bradshaw (unpublished).
[36] P.Z. Rashev, K.L. Bowes, and M.P. Mintchev, IEEE Trans. Inf. Technol. Biomed. **6**, 296 (2002).
[37] L. A. Bradshaw, Ph.D. dissertation, Vanderbilt University, 1995 (unpublished).
[38] A.C. Barnard, I.M. Duck, M.S. Lynn, and W.P. Timlake, Biophys. J. **7**, 463 (1967).
[39] J. Sarvas, Phys. Med. Biol. **32**, 11 (1987).
[40] M.S. Hämäläinen, R. Hari, R.J. Ilmoniemi, J. Knuutila, and O.V. Lounasmaa, Rev. Mod. Phys. **65**, 413 (1993).
[41] M.S. Hämäläinen and J. Sarvas, Phys. Med. Biol. **32**, 91 (1987).
[42] V. S. Vladimirov, *Equations of Mathematical Physics* (Marcel Dekker, New York, 1971).
[43] L.A. Bradshaw, W.O. Richards, and J.P. Wikswo, Jr., IEEE Trans. Biomed. Eng. **50**, 836 (2003).
[44] R.M. Arthur and D.B. Geselowitz, IEEE Trans. Biomed. Eng. **17**, 141 (1970).