Optics Letters

On the equivalence of speckle contrast-based and diffuse correlation spectroscopy methods in measuring *in vivo* blood flow

K. Murali,[1] A. K. Nandakumaran,[2] and Hari M. Varma[1,*]

[1]Department of Biosciences and Bioengineering, Indian Institute of Technology, Bombay, India
[2]Department of Mathematics, Indian Institute of Science, Bangalore, India
*Corresponding author: harivarma@iitb.ac.in

Received 20 May 2020; revised 17 June 2020; accepted 22 June 2020; posted 22 June 2020 (Doc. ID 397979); published 13 July 2020

We establish the equivalence between laser speckle contrast-based and diffuse correlation spectroscopy methods in *in vivo* imaging of blood flow using the Volterra integral equation theory. We further substantiate the need of regularized fitting while employing the multiexposure speckle contrast imaging to recover autocorrelation function.

https://doi.org/10.1364/OL.397979

Laser speckle contrast imaging (LSCI) is a full-field imaging technique that quantifies the surface blood flow (<1 mm depth) by uniformly illuminating the surface of tissue with a laser and imaging it with a camera [1]. A multiexposure-based speckle contrast imaging system, shortly termed as MESI, is used to quantify the absolute blood flow, by fitting the multiexposure speckle contrast against appropriate single scattering models [2]. On the other hand, deep tissue blood flow is quantified using diffuse wave spectroscopy (DWS) or diffuse correlation spectroscopy (DCS), with a focused laser source illumination and avalanche photodiode (APD) or photomultiplier tube (PMT), employed to measure intensity speckles [3,4]. Here, large source detector (SD) separations (few centimeters) are often employed to collect the diffused photons. The normalized autocorrelation of the intensity speckles, g_2, is related to the deep tissue blood flow through correlation diffusion equation (CDE) [3,4].

In order to reduce the complexity of measurement system and expenses associated, simultaneous measurement of several speckles using array detectors like charge-coupled device (CCD)/complementary metal–oxide semiconductor (CMOS) or single-photon avalanche diode (SPAD) cameras have been used in methods like diffuse speckle contrast analysis (DSCA) [5] and speckle contrast optical spectroscopy (SCOS) [6]. SCOS utilizes multidistance and multiexposure speckle contrast data to measure deep tissue blood flow in the human hand [6] and adult human brain [7]. Several works are reported recently in employing high frame rate CCD/CMOS/SPAD cameras to directly measure the intensity autocorrelation for both surface and deep tissue blood flow [8–11]. All these methods rely upon the high frame rate of the camera to compute autocorrelation of the intensity speckles captured by each pixel of the camera.

All the above-mentioned work establishes the fact that both speckle contrast and intensity autocorrelation carry information about the blood flow although the equivalence of the two approaches is not well-studied. In other words, is it possible to recover either of the two quantities, i.e., speckle contrast or intensity autocorrelation, given the other? This was addressed partially via an experimental and computational approach in [12,13], where a low frame rate camera (<100 frames per second) has been used to measure both the surface and deep tissue blood flow by recovering the autocorrelation function from multiexposure speckle contrast data. Although it is easy to compute the speckle contrast from the measured intensity autocorrelation, the recovery of the intensity autocorrelation from speckle contrast is not trivial.

In this work, using Volterra integral equation (VIE) theory, we establish the fact that under certain conditions on the speckle contrast data, the recovery of blood flow using both speckle contrast and field/intensity autocorrelation is equivalent. In other words, we show that given multiexposure speckle contrast data, it is possible to uniquely recover the field autocorrelation. We also establish the need of Tikhonov regularization to solve this problem due to the associated ill-posedness in the sense of Hadamard.

The relation connecting speckle contrast, κ, to the normalized field autocorrelation, g_1, is given by [14]

$$\kappa^2(r, T) = \frac{2\beta}{T}\int_0^T \left(1 - \frac{\tau}{T}\right) g_1^2(r, \tau)\mathrm{d}\tau. \quad (1)$$

Here r is the SD separation, T is the camera exposure time, τ is the correlation delay time, and β is a constant that depends on the collection optics. Although g_1 depends on every SD separation, the following analysis is independent of r; hence, we drop this variable from Eq. (1). The speckle contrast-based flow measurement utilizes either single or multiexposure speckle contrast data. A direct fit of the measured multiexposure or multidistance speckle contrast against theoretical flow models to quantify blood flow is usually attempted. In order to analyze whether this is equivalent to the correlation measurement, where g_2 (or g_1 via Siegert relation) can be measured directly, we pose the following question: is it possible to recover the function

g_1 for all τ, given the multiexposure speckle contrast data? Using the theory of VIE, we prove that it is indeed possible. To comply with the standard notations of the VIE theory, we adopt a slight change in notations, to rewrite the Eq. (1), in the form of VIE of first kind, which is

$$\kappa^2(T) = 2\beta \int_0^T K(T, \tau) u(\tau) \mathrm{d}\tau, \tag{2}$$

where the kernel is defined as $K(T, \tau) \equiv \frac{1}{T} - \frac{\tau}{T^2}$ and $u \equiv g_1^2$. The VIE theory states the conditions under which the function u can be retrieved for all correlation delay, τ, given the data, κ, for all exposure times, T. The existence and uniqueness of VIE of first kind are proved by converting it into VIE of second kind and applying the theorem below:

Theorem 1: Let $I = [0, M]$ and $D = \{(T, \tau) : 0 \le \tau \le T \le M\}$. Let $\kappa \in C(I)$ and $K \in C(D)$, i.e., both the data and the kernel are continuous functions in appropriate domains. Then, there exists a unique solution $u \in C(I)$ to VIE of second kind.

Proof: For proof please, see Theorem 1.2.3 in page 5 of Ref. [15].

In order to apply above theorem to Eq. (2), we have to convert the VIE of first kind to that of second kind by differentiating Eq. (2), with respect to T. Additionally, we need other conditions to be followed on both data, κ, and Kernel, K. We first consider the condition that $\kappa(0) = 0$, which is required to satisfy the continuity of the data at the origin. The following result shows that it is in indeed not satisfied.

Lemma 1: Given the relation in Eq. (2), we have $\lim_{T\to 0} 2\int_0^T K(T, \tau) u(\tau) \mathrm{d}\tau = u(0)$.

Proof: Let u be continuous at origin, which implies, for a given $\epsilon > 0$, there exists a $t_0 \in I$ such that $|u(\tau) - u(0)| \le \epsilon$ for all $0 \le \tau \le t_0$. Since $\frac{2}{T^2}\int_0^T (T - \tau) u(0) \mathrm{d}\tau = u(0)$, we have

$$\left| \frac{2}{T^2} \int_0^T (T - \tau)(u(\tau) - u(0)) \mathrm{d}\tau \right| \le \frac{2\epsilon}{T^2} \int_0^T (T - \tau) \mathrm{d}\tau = \epsilon.$$

The above result gives $\kappa^2(0) = \beta u(0) \neq 0$ because $u(0) = g_1^2(0) = 1$. Hence, we modify the left-hand side of Eq. (2) to $\tilde{\kappa}(T) \equiv T^2\kappa^2(T)$, for which $\lim_{T\to 0} \tilde{\kappa} = 0$. With the new kernel, $\tilde{K}(T, \tau) \equiv T - \tau$, we have the modified version of Eq. (2),

$$\tilde{\kappa} = 2\beta \int_0^T \tilde{K}(T, \tau) u(\tau) \mathrm{d}\tau. \tag{3}$$

Theorem 2: Let $u \in C(I)$, $\tilde{\kappa} \in C^2(I)$, and $\tilde{\kappa}(0) = \frac{d\tilde{\kappa}}{dT}(0) = 0$. Then, Eq. (3) has a unique solution $u \in C(I)$.

Proof: Differentiate Eq. (3) with respect to T to get

$$\frac{d\tilde{\kappa}}{dT} = 2\beta \frac{d}{dT} \int_0^T \tilde{K}(T, \tau) u(\tau) \mathrm{d}\tau$$

$$= 2\beta \left(\tilde{K}(T, T) u(T) + \int_0^T u(\tau) \mathrm{d}\tau \right) = 2\beta \int_0^T u(\tau) \mathrm{d}\tau.$$

Since the Kernel is zero for $T = \tau$, i.e., $\tilde{K}(T, T) = 0$, we cannot apply Theorem 1 directly; hence, we proceed to differentiate Eq. (3) once again to get

$$\frac{d^2\tilde{\kappa}}{dT^2} = 2\beta \frac{d}{dT} \int_0^T u(\tau) \mathrm{d}\tau = 2\beta u(T), \tag{4}$$

and the existence of unique solution follows from Theorem 1. The Eq. (1) can be modified, through Siegert's relation [4], as $\kappa^2(T) + 1 = \frac{2}{T}\int_0^T (1 - \frac{\tau}{T}) g_2(\tau) \mathrm{d}\tau$. All the above observations and results are equally applicable to this equation as well.

The additional conditions on the data that is $\tilde{\kappa} \in C^2(I)$ (i.e., both $\frac{d\tilde{\kappa}}{dT}$ and $\frac{d^2\tilde{\kappa}}{dT^2}$ exist and are continuous) such that $\tilde{\kappa}(0) = \frac{d\tilde{\kappa}}{dT}(0) = 0$ are essential to guarantee a unique solution for this problem. Thus, the condition under which the multiexposure speckle contrast data can uniquely recover the field autocorrelation is that the data should be twice differentiable in domain I. In fact, if u is a continuous function, i.e., $u \in C(I)$, then by the fundamental theorem of calculus, $\tilde{\kappa}$ is continuous and differentiable, which, in turn, implies $\tilde{\kappa} \in C^2(I)$. Additionally, the multiexposure data κ should be modified to $\tilde{\kappa}$ in order to satisfy the continuity at the origin. As evident from the proof, an equivalent problem to Eq. (3) is the second-order ordinary differential equation in $\tilde{\kappa}$, i.e., $\frac{d^2\tilde{\kappa}}{dT^2} = 2\beta u(T)$ with two initial conditions $\tilde{\kappa}(0) = \frac{d\tilde{\kappa}}{dT}(0) = 0$. However, this formulation is seldom used for the numerical inversion due to the presence of noise as discussed below.

We now consider the ill-posedness associated with this problem in the sense of Hadamard [15,16]. The additional conditions on the data, which are $\tilde{\kappa}(0) = \frac{d\tilde{\kappa}}{dT}(0) = 0$, indicate the need of continuity at the origin. This condition is often violated as the camera is often associated with electronic noise at the lower exposures. It is clear from Eq. (4) that u is second-order differential of the multiexposure speckle contrast data, which implies that the presence of noise will severely affect the retrieval of field autocorrelation. The class of VIEs with kernel such that $\tilde{K}(T, T) = 0$ and $\frac{\partial \tilde{K}}{\partial T}(T, T) \neq 0$ are called μ-smoothening problems with $\mu = 2$. With a larger value of μ, the associated ill-posedness is larger. Hence, this problem is posed in the integral form itself as given in Eq. (3) and is solved using Tikhonov regularization. The Tikhonov regularized problem seeks the solution for

$$\lambda(u(T) - u_p) + 2\beta \int_0^T \tilde{K}(T, \tau) u(\tau) \mathrm{d}\tau = \tilde{\kappa} + N, \tag{5}$$

where λ is the regularization parameter and N is the measurement noise. In [12], we have experimentally found that the Tikhonov regularized problem to recover field aurocorrelation is still numerically unstable and requires prior, which is $u_p \equiv u(0) = g_1^2(0) = 1$. The convergence analysis of Tikhonov regularized μ-smoothening problem with *a priori* information is extensively studied in the [17,18].

We show the above-mentioned facts numerically by performing two simulation studies, one for surface blood flow and other for deep tissue blood flow imaging. Here, the autocorrelation functions used were $g_1(\tau) = \exp(-\frac{\tau}{\tau_c})$ (with $\tau_c = 0.5$ ms) for the superficial blood flow and $g_1(\tau) = \frac{\exp(-\sqrt{a+b\tau}r)}{\exp(-\sqrt{(a)}r)}$ for the multiple scattering case (parameters $a = 3.6\ \mathrm{cm}^{-2}$ and $b = 7.2327 \times 10^4\ \mathrm{cm}^{-2}/\mathrm{s}$ were chosen based on typical optical and dynamical properties of the tissue, and SD separation was chosen to be $r = 2$ cm). The function g_1 in both cases belongs to $C(I)$ and, hence, $\tilde{\kappa} \in C^2(I)$, which can also be easily verified analytically by substituting $u = g_1^2$ in Eq. (3). The multiexposure speckle contrast was generated numerically for 250 exposure times ranging from 10^{-5} s to 10^{-2} s

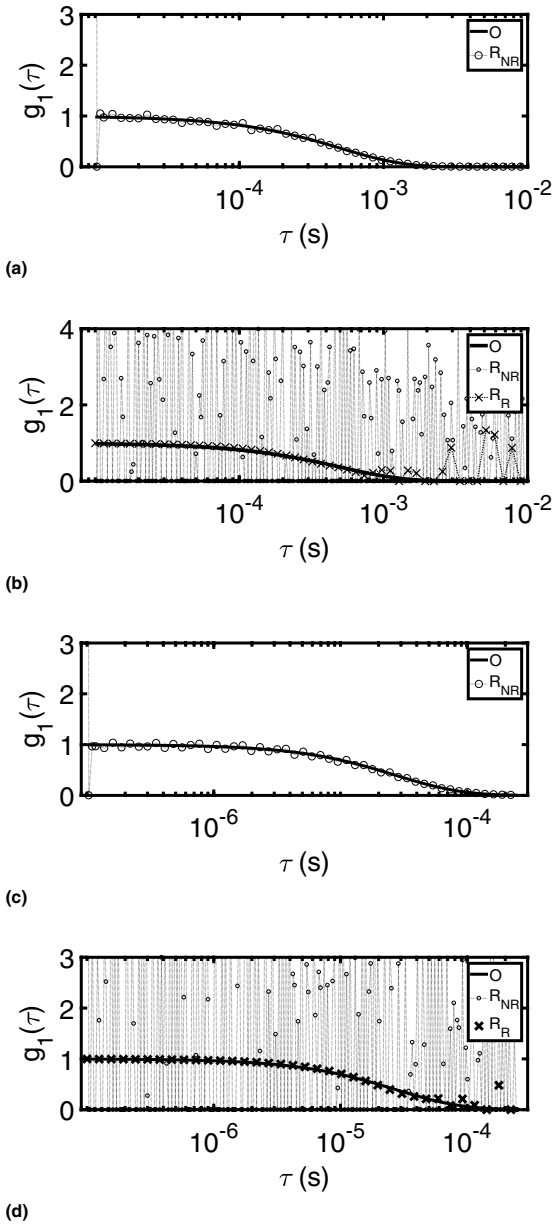

Fig. 1. Legend: O, original g_1; R_{NR}, recovered g_1 without regularization; R_R, recovered g_1 with regularization; (a) and (b) correspond to the single scattering model while (c) and (d) correspond to the multiple scattering model. In (a) and (c), the original and recovered g_1 are shown and are comparable to one another. Note that in this case, speckle noise was not added to speckle contrast data. In (b) and (d), the original and recovered g_1 is shown in the case, where speckle noise was added to multiexposure speckle contrast data. It can be seen that when regularization was not used, the g_1 recovered does not match with original g_1, and in the case when regularization was used, g_1 is comparable to that of the original g_1.

and 10^{-7} s to 0.24 ms for single scattering and multiple scattering models, respectively. Speckle noise was added by using the noise model given in [19], where the standard deviation is $\sigma_\kappa = \kappa(\sqrt{\kappa^2 + 0.5})/\sqrt{P}$. Here, P is the number of samples (camera pixels), which is taken to be 50,000 for this simulation. Using a mutistep method [12,20], we discretize Eq. (3), and the resulting linear system of equations was solved by Tikhonov regularization as defined in Eq. (5). The results are shown in Fig. 1, where Figs. 1(a) and 1(b) correspond to results from single scattering model and Figs. 1(c) and 1(d) correspond to multiple scattering model. Figures 1(a) and 1(c) show the comparison between original and recovered g_1, without noise being added to speckle contrast. This shows that the measurements obtained by speckle contrast-based methods and those of DCS are comparable to one another establishing the equivalence. Note that there is no regularization or *a priori* information used in this case. The mismatch in the initial portion of the recovered g_1 is due to the error caused by numerical integration. Figures 1(b) and 1(d) show the cases when noise was added to speckle contrast, which distorts the recovered g_1 in both the cases. It can also be seen that, when regularization was used with prior information ($u_p = 1$ for all τ), the recovered g_1 from multiexposure speckle contrast data is comparable to that of the original g_1. At larger values of τ, g_1 tends to zero, which implies that speckle contrast also tends to zero as exposure time becomes larger. However, in practice, due to domination of noise in speckle contrast for larger exposure times, the recovered g_1 is distorted for larger values of τ. This shows the need of regularization and prior information in the presence of noise.

Funding. Indian Institute of Technology Bombay (Seed grant); Department of Science and Technology, Ministry of Science and Technology, India (SERB–Early career research award); Department of Biotechnology, Ministry of Science and Technology, India (Ramalingaswamy Fellowship-2016).

Disclosures. The authors declare no conflicts of interest.

REFERENCES

1. J. Briers and A. Fercher, Invest. Ophthalmol. Visual Sci. **22**, 255 (1982).
2. A. B. Parthasarathy, W. J. Tom, A. Gopal, X. Zhang, and A. K. Dunn, Opt. Express **16**, 1975 (2008).
3. D. A. Boas, L. Campbell, and A. G. Yodh, Phys. Rev. Lett. **75**, 1855 (1995).
4. T. Durduran, R. Choe, W. Baker, and A. G. Yodh, Rep. Prog. Phys. **73**, 076701 (2010).
5. R. Bi, J. Dong, and K. Lee, Opt. Lett. **38**, 1401 (2013).
6. C. P. Valdes, H. M. Varma, A. K. Kristoffersen, T. Dragojevic, J. P. Culver, and T. Durduran, Biomed. Opt. Express **5**, 2769 (2014).
7. T. Dragojević, J. L. Hollmann, D. Tamborini, D. Portaluppi, M. Buttafava, J. P. Culver, F. Villa, and T. Durduran, Biomed. Opt. Express **9**, 322 (2018).
8. H.-J. Jeon, M. M. Qureshi, S. Y. Lee, J. D. Badadhe, H. Cho, and E. Chung, Sci. Rep. **9**, 1 (2019).
9. D. D. Postnov, J. Tang, S. E. Erdener, K. Kilic, and D. A. Boas, "Dynamic laser speckle imaging," https://www.biorxiv.org/content/10.1101/626515v1.full.
10. M. M. Qureshi, J. Brake, H.-J. Jeon, H. Ruan, Y. Liu, A. M. Safi, T. J. Eom, C. Yang, and E. Chung, Biomed. Opt. Express **8**, 4855 (2017).
11. J. D. Johansson, D. Portaluppi, M. Buttafava, and F. Villa, J. Biophoton. **12**, e201900091 (2019).
12. K. Murali, A. Nandakumaran, T. Durduran, and H. M. Varma, Biomed. Opt. Express **10**, 5395 (2019).
13. K. Murali and H. M. Varma, in *Optical Tomography and Spectroscopy* (Optical Society of America, 2020), paper STu4D–7.
14. R. Bandyopadhyay, A. Gittings, S. Suh, P. Dixon, and D. J. Durian, Rev. Sci. Instrum. **76**, 093110 (2005).
15. H. Brunner, *Volterra Integral Equations: An Introduction to Theory and Applications* (Cambridge University, 2017), Vol. **30**.
16. C. R. Vogel, *Computational Methods for Inverse Problems* (SIAM, 2002), Vol. **23**.

17. V. Sergeev, *Doklady Akademii Nauk* (Russian Academy of Sciences, 1971), Vol. **197**, pp. 531–534.
18. P. K. Lamm, *Surveys on Solution Methods for Inverse Problems* (Springer, 2000), pp. 53–82.
19. S. Yuan, *Sensitivity, Noise and Quantitative Model of Laser Speckle Contrast Imaging* (Tufts University, 2008).
20. C. Andrade, N. B. Franco, and S. McKee, Computing **27**, 189 (1981).