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A Simulation Study of the Variability of Indocyanine Green Kinetics and Using Structural *a priori* Information in Dynamic Contrast Enhanced Diffuse Optical Tomography (DCE-DOT)

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Abstract

We investigated 1) the variability of the indocyanine green kinetics (ICG) between different cases in the existence of random noise changing the size of the imaging region, the location and the size of the inclusion, 2) the use of structural *a priori* information to reduce the variability. We performed two dimensional simulation studies for this purpose. In the simulations, we used a two-compartmental model to describe the ICG transport and obtained pharmacokinetic parameters. The transfer constant and the rate constant showed a wide variation i.e. 60% and 95% respectively when random Gaussian noise with a standard deviation of 1% in amplitude and 0.4 degrees in phase was added to data. Moreover, recovered peak ICG concentration and time to reach the peak concentration was different within different cases. When structural *a priori* information was used in the reconstructions, **the variations in the transfer and the rate constant** were reduced to 29%, 15%, **respectively**. As a result, although the recovered peak concentration was still case dependent, the variability of the shape of the kinetic curve was reduced.

Keywords

Dynamic imaging; diffuse optical tomography; contrast enhancement; indocyanine green; two-compartmental model; reconstruction; computer simulation

1. Introduction

Diffuse optical tomography (DOT) can detect the abnormalities in the tissue due to endogenous contrast changes (Gibson *et al* 2005). For example, in the cancerous breast tissue, the endogenous absorption contrast arises due to different hemoglobin content of the tumor. An additional contrast mechanism is the change in the cellular and organelle density and size. These cellular and subcellular changes cause an increase in the scattering properties of the diseased region (Thomsen and Tatman 1998, Mourant *et al* 1998). It is well established that the endogenous contrast changes can be up to two or three times higher than the healthy tissue (Cerussi *et al* 2006). Still, it would be desirable to use exogenous contrast agents in order to increase the contrast between the healthy and diseased tissue. **This results** in a better characterization and localization of the abnormalities, very much like in the field of nuclear imaging and magnetic resonance imaging (MRI).

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In the Near Infrared (NIR) range, the most widely used contrast agent is indocyanine green (ICG). It is approved by the FDA and has been used in the medical field since 1956. ICG is a blood pool agent that binds to plasma proteins (Yoneya *et al* 1998), therefore, it is confined to the vascular compartment and behaves as a macromolecular contrast agent with a low vascular permeability. The transport rate of the contrast agent between extravascular and intravascular space is determined by the permeability of the microvessels, their surface area, and blood flow. It has been demonstrated that the ICG has different wash-in and wash-out properties between benign and malignant tumors (Ntziachristos *et al* 2000, Intes *et al* 2003). For example, malignant tumors exhibit a slower wash-out rate compared to benign tumors and normal tissue.

Dynamic contrast enhanced diffuse optical tomography (DCE-DOT) allows the study of kinetics of the ICG in tumors and normal tissue. The data are composed of a series of images acquired before and after the injection of the ICG. Measured optical flux can be used to generate images of the ICG concentration vs. time, $C(t)$, that can be evaluated to extract physiological parameters. Absorption contrast enhancement can be analyzed using a two-compartmental pharmacokinetic model that is described by Tofts and Kermode (1991).

In recent years, there have been several theoretical and experimental studies of the kinetics of the ICG in the tissue. Gurfinkel *et al* (2000) presented a double exponential, four-parameter model to describe uptake of the ICG and employed a fluorescence reflectance imaging system for the measurements in small animal models. However, they did not detect a difference in the ICG uptake rates between the normal and the neoplastic tissue. Later, Cuccia *et al* (2003) used a six-parameter pharmacokinetic model and presented a study of the dynamics of the ICG in an adenocarcinoma rat tumor model by the use of diffuse optical spectroscopy coregistered with MRI. They found differences in the ICG uptake between necrotic and edematous tumors. Ntziachristos *et al* (2000) reported the first results on the uptake of the ICG *in vivo* in the human breast. In their study, a concurrent MRI and frequency domain DOT examination of the human breast was performed. Intes *et al* (2003) investigated the uptake of ICG by breast tumors using a continuous wave DOT system. Alacam *et al* (2005) and Alacam *et al* (2006a) used an extended Kalman filter scheme to analyze small-animal ICG pharmacokinetics data given in Cuccia *et al* (2003). Alacam *et al* (2006b) presented a study in three breast cancer patients. They observed differences in the ICG concentration in plasma and the extravascular compartments.

In parallel to recent developments in nano-oncology, optical imaging systems that can monitor changes in absorption and scattering simultaneously have become very attractive (Ferrari 2005, Jain 2005, Yezhelyev *et al* 2006). **Please** note that, nano particles usually cause strong scattering due to their high-cross section. Monitoring scattering might be useful in detection of low **particle concentrations** (Malicka *et al* 2003). In addition, there has been extensive work on metal enhanced ICG that can increase the optical absorption and scattering contrast simultaneously (Malicka *et al* 2003). Although these developments are currently in infant stage, it is highly possible that sophisticated optical imaging methods will be very useful for application of nanotechnology in cancer research.

The major obstacles on the road to the use of DOT in tumor diagnosis are its low spatial resolution and limited depth penetration (Pogue *et al* 2000, Song *et al* 2002, Pogue *et al* 2002, Pogue *et al* 2006). Moreover, DOT inverse problem is ill-posed. As a result, the accuracy of the recovered optical parameters depends on the level of noise. In this study, we performed several simulation studies to find the corresponding effects of these limitations on the calculation of the physiological parameters that were calculated from the ICG kinetic curve. A two-compartmental model was used to simulate the dynamics of ICG. We also investigated the effects of the use of structural priors on the calculation of the physiological parameters. Note that, the use of structural *a priori* information in DOT reconstruction has been widely

discussed in the literature and it requires the segmentation of the discretization domain into regions (Dehghani *et al* 2006, Dehghani *et al* 2003b, Brooksby *et al* 2005, Li *et al* 2003, Li *et al* 2007, Intes *et al* 2004). This procedure makes it possible to use some spatial constraints in the inverse problem and, as a result, an accurate determination of the average static optical parameters in segmented regions can be achieved.

2. Methods

2.1. Modeling of ICG Kinetics

ICG transport in tissue can be described using a two compartmental model given by Tofts and Kermode (1991), Cuccia *et al* (2003). The model consists of an intravascular (or plasma) compartment and an extravascular compartment. Extravascular compartment is the leakage space within the interstitial space of the tissue.

Net flow into the extravascular compartment is

$$\frac{dC_e}{dt} = K^{trans} C_p - k_{ep} C_e \quad (1)$$

where C_p and C_e are the contrast agent concentrations in the plasma and extravascular compartment, **respectively**. $K^{trans}(sec^{-1})$ is the transfer constant that defines the flux rate between the blood plasma and the extravascular compartment. The rate constant $k_{ep}(sec^{-1})$ describes the back flux from the extravascular compartment to the blood plasma. These parameters are related to each other by the equation, $k_{ep} = K^{trans}/v_e$ where v_e is the extravascular compartment fractional volume.

The net flow from the plasma to the extravascular compartment and kidneys/liver can be approximated by a biexponential decay:

$$C_p(t) = A_1 \exp(-\alpha_1 t) + A_2 \exp(-\alpha_2 t) \quad (2)$$

where A_1, A_2 (μM) are the amplitudes of the exponential components, and α_1 and α_2 (sec^{-1}) are their rate constants.

The total ICG concentration, C_t , measured by the DOT system is a linear combination of the plasma (or intravascular) and the extravascular concentration

$$C_t = v_p C_p + v_e C_e \quad (3)$$

where v_p is the plasma fractional volume.

The solution of the equations (1) –(3) is given as (Cuccia *et al* 2003)

$$\begin{aligned} C_t(t) &= A_1 \left(v_p + \frac{K^{trans}}{k_{ep} - \alpha_1} \right) \exp(-\alpha_1 t) \\ &+ A_2 \left(v_p + \frac{K^{trans}}{k_{ep} - \alpha_2} \right) \exp(-\alpha_2 t) \\ &- \left(A_1 \left(\frac{K^{trans}}{k_{ep} - \alpha_1} \right) + A_2 \left(\frac{K^{trans}}{k_{ep} - \alpha_2} \right) \right) \exp(-k_{ep} t). \end{aligned} \quad (4)$$

The rate constants k_{ep} and K^{trans} are expected to be different for benign and malignant breast tumors due to increased leakiness of the blood vessels in malignant tumors (Knopp *et al*

1999). In order to obtain these parameters, first, the ICG concentration must be calculated from optical measurements. Then, the change in the absorption coefficient, $\delta\mu_a$, can be related to the injected ICG concentration, δC , as:

$$\delta\mu_a = 2.3\varepsilon\delta C \quad (5)$$

where ε is the extinction coefficient of the ICG. Then, a data fitting algorithm such as nonlinear least squares can be used to fit the calculated concentrations from equation (5) to equation (4).

2.2. Modeling of Forward and Inverse Problems

Spatially resolved absorption and scattering coefficients at different time points can be calculated from the DOT measurements by solving the inverse problem. In order to model the light transport in tissue, we use the diffusion equation. The frequency domain representation of the diffusion equation for tissue is written as (Arridge *et al* 1999),

$$\nabla \cdot \mathbf{D}(\mathbf{r}) \nabla \phi(\mathbf{r}, \omega) - (\mu_a(\mathbf{r}) + \frac{i\omega n}{c_0}) \phi(\mathbf{r}, \omega) = -S(\mathbf{r}, \omega) \quad (6)$$

where $\phi(\mathbf{r}, \omega)$ is the optical light fluence rate ($W.mm^{-2}$), $S(\mathbf{r}, \omega)$ is the optical light source ($W.mm^{-3}$), ω is the optical light source modulation frequency, $D(\mathbf{r})$ is the photon diffusion coefficient, μ_a is the photon absorption coefficient, c_0 is the speed of the light in vacuum, and n is the index of refraction of the medium. The diffusion coefficient is given as,

$$D(\mathbf{r}) = \frac{1}{3[\mu_a(\mathbf{r}) + \mu'_s(\mathbf{r})]} \quad (7)$$

where μ'_s is the reduced scattering coefficient.

Robin boundary condition (RBC) relates the optical fluence rate to optical flux at the boundary and can be written as

$$\phi(\xi, \omega) - 2AF(\xi, \omega) = 0 \quad (8)$$

where the optical flux $F(\xi, \omega) = -D(\mathbf{r})\mathbf{n} \cdot \nabla \phi(\xi, \omega)$, ξ is any point on the boundary $\partial\Omega$ of the domain Ω , $\mathbf{n}$ is the outward normal vector for the boundary, and A is a constant that accounts for the internal reflection of light due to the index of refraction mismatch.

The inverse problem for the DOT is an estimation of the optical parameters by minimizing the error between the measured and calculated data:

$$\chi(\mu)^2 = \sum_i^M (\phi_{m,i} - \phi_{c,i}(\mu))^2 \quad (9)$$

where ϕ_m is the measured data, ϕ_c is the calculated data using the forward solver, M is the total number of source-detector combinations, and $\mu = \{\mu_a, \mu'_s\}$. In order to find the minimum of the error function, the derivative is equated to zero and then the solution is expanded in a truncated Taylor series (Paulsen and Jiang 1995). The matrix equation to be solved can be written as

$$\Delta \mu = (\mathbf{J}^T \mathbf{J} + \lambda \mathbf{I})^{-1} \mathbf{J}^T (\phi_m - \phi_c) \quad (10)$$

where $J_{ij} = \frac{\partial \phi_{c,i}}{\partial \mu_j}$ is the Jacobian matrix that can be calculated using the adjoint method (Arridge and Schweiger 1995), $\Delta \mu$ is the update vector that is the difference between the true value and the estimated value of either absorption or reduced scattering coefficient, $\mathbf{I}$ is the identity matrix and λ is the regularization parameter.

The equation (10) can be solved iteratively. The regularization parameter is selected as (?)

$$\lambda_i = \frac{\text{Tr}((\mathbf{J}^T \mathbf{J})_i) \text{norm}(\chi_i)}{N \text{norm}(\chi_1)} \quad (11)$$

where i is the iteration number, Tr represents the trace of a matrix, and N is the number of unknowns. χ_1 is the norm of the error in the first iteration. This empirical method provides a very fast and efficient way of selecting the regularization parameter in each iteration. The iterations were stopped when χ_2 error changed less than 2 % between iterations.

The incorporation of the structural *a priori* information in the DOT reconstruction can be accomplished in several ways. We use *a priori* information in three steps in the reconstruction. Initially, the finite element mesh is segmented into a background region and a region of interest (ROI). In the first step, the initial optical parameters for different regions are found using a non-linear least square estimate algorithm (built in `lsqnonlin` function of MATLAB). Please note that if *a priori* is not available, homogenous fitting is done to find the initial values. In the second step, a two-region regularization method is employed. The selection of λ values can be achieved modifying the equation (11) for multiple regions.

$$\lambda_i^r = \frac{\text{Tr}((\mathbf{J}^T \mathbf{J})_i^r) \text{norm}(\chi_i)}{N^r \text{norm}(\chi_1)} \quad (12)$$

where r denotes the region number, $\text{Tr}((\mathbf{J}^T \mathbf{J})_i^r)$ is the sum over the diagonal elements **that belong** to the region r and N^r is the number of unknowns corresponding to that region.

As the third step, the mean value of the optical parameters in each region is assigned to all elements in that region at the end of each iteration. As a result, the value of reconstructed optical parameters are very accurate as long as the boundaries of the regions are selected accurately. In determination of the ICG kinetics curves, structural *a priori* knowledge can be used to increase the spatial resolution and the accuracy of the reconstructed ICG concentration.

We use the finite element method (FEM) to solve the forward problem. The simulated measurement data was generated solving the forward problem on a fine mesh of 6785 nodes and 13056 elements. Then, a dual mesh scheme was used for all the reconstructions. The forward problem to obtain the fluence rate was solved on a mesh of 1761 nodes and 3264 first order triangular elements. A denser element distribution was used underneath the boundary to improve the accuracy close to measurement points. The sources were placed at a location $1/\mu'_s$ below the surface. A coarse mesh with 289 nodes and 512 elements was generated for the reconstruction basis in order to reduce the number of unknowns.

2.3. Numerical Experiments

There are six simulations corresponding to different cases. We use a simplified notation to present different situations. (D,d,r) denotes a D -mm-diameter circular region with a d -mm-diameter target located r mm off-center (Figure 1a): e.g. (100,15,0) shows the case in which a 100-mm-diameter circular region with a 15-mm-diameter target located at the center of the circular region.

In **all** cases, the time resolution was set to 16 seconds for 64 measurements. The number of simulated time points was 20. The parameters were selected as: $D = \{80, 100\}$ mm, $d = \{8, 15\}$ mm, and $r = \{0, 25\}$ mm. The background optical properties were set as $\mu_a = 0.006$ mm⁻¹, $\mu'_s = 0.8$ mm⁻¹, and $n = 1.4$. The pre-ICG optical properties of the target were set to $\mu_a = 0.009$ mm⁻¹, $\mu'_s = 1.2$ mm⁻¹, and $n = 1.4$. Single wavelength, 785 nm, and single modulation frequency, 100 MHz, were used in the simulations. Gaussian noise, 1% amplitude-noise and 0.4 degrees-phase-noise, was added to the measurement vectors in accordance with the noise levels of our experimental system. The simulated measurement data was generated by simulating a time dependent ICG concentration (Figure 1b) that caused a time dependent absorption coefficient (Figure 1c) in the ROI. **Please note that the change in scattering due to the ICG was negligible** and therefore μ'_s was assumed to be constant during the simulated measurements. In order to generate the ICG kinetics, the physiological parameters k_{ep} , K^{Trans} , A_1 , A_2 , v_p , α_1 , α_2 were set to 1.56 min⁻¹, 0.348 min⁻¹, 1.5 μ M, 2 μ M, 0.0142, 1 min⁻¹, 0.1 min⁻¹, respectively (Cuccia *et al* 2003).

Absorption coefficient at **each time point** was calculated from the DOT measurements by solving the inverse problem with and without *a priori* information. We used anatomical *a priori* information to divide the domain of interest into two distinct regions, 1) region of interest (ROI), 2) background. Then, a non-linear least squares method was used to fit the calculated concentrations within the ROI to equation (4) in order to obtain the physiological parameters. In the fitting, plasma curve rate constants and amplitudes α_1 , α_2 , A_1 , and A_2 were fixed to 1 min⁻¹, 0.1 min⁻¹, 1.5 μ M, 2.0 μ M, respectively. These values were selected approximately from (Shinoraha *et al* 96). **Finally, the parameters k_{ep} , K^{Trans} , and v_p were fitted** in the equation (4).

3. Results

Initially, we performed the reconstructions for the baseline for all six cases. In baseline simulations, absorption coefficient was static in time and scattering map was also reconstructed. For example, Figure 2 shows the reconstructed optical parameter maps for the simulated baseline data for (80,15,25) case. The reconstructions were performed without (second row) and with (third row) structural priors. The errors in the calculated maximum values of μ_a and μ'_s in the ROI were within 5% of the true value **for both cases**.

In the next step, the dynamic simulations were performed for all cases to calculate the absorption coefficient at each time point in the ROI. For example, Figure 3 shows the reconstructed optical parameter maps at three time points for the simulated dynamic data for (80,15,25) case. The reconstructions were performed without (first row) and with (second row) structural priors.

Afterwards, we calculated the peak ICG concentration, K^{trans} , k_{ep} , and v_p for each case. The peak concentrations of the inclusions had large errors (Table 1). For example, the fitting of the peak concentration resulted 66% error in (80, 15, 25) case, 84% error in (100, 8, 25) and 58% error in (80, 15, 0) case. However, when the structural priors were used, the errors reduced to 6%, 39% and 1% respectively. On the other hand, the peak concentration values were different for each case and the reconstructions **revealed** different peaks although the true peak was same

for all (Figure 4). This was an expected result and showed that the calculated peak concentration was dependent on the size and the location of the inclusion as well as the size of the imaging region.

In Table 2, the calculated fitting parameters and the corresponding standard deviations and the coefficient of variations are summarized. In this case, no structural priors were used in the calculation of absorption coefficient. The fitting results ranged from 0.0112 to 0.0793 (sec^{-1}) for k_{ep} and from 0.0008 to 0.0032 sec^{-1} for K^{trans} . For example, the fitted values of k_{ep} and K^{trans} were 0.0147 sec^{-1} and 0.0009 sec^{-1} respectively for (80, 15, 25) case. We also calculated the coefficient of variation that was defined as standard deviation divided by mean. The coefficients of variation for k_{ep} , K^{trans} , and v_p were 60%, 95%, and 114% respectively. Note that, huge variations in the ICG curves could be seen in the first row of the Figure 4. Especially, the time to reach the peak ICG concentration for 8-mm inclusion and 15-mm inclusion were very different. However, the coefficients of variation for k_{ep} , K^{trans} , and v_p were reduced to 29%, 15%, 93% when the *a priori* information was used in the DOT reconstruction (Table 3). As a result, when the ICG curves were normalized with respect to their maximum values, they overlaid on top of each other (the second row of Figure 4). This showed that the use of structural priors reduced the effects of random and systematic errors on the calculation of ICG curves and the rising and the descending slopes were independent of target size, location, and size of the imaging region. Note that v_p was not improved much when the structural priors were used. Therefore it might be useful to calculate this value using the baseline as suggested by Cuccia *et al* (2003).

4. Discussion and Conclusions

In summary, we performed simulation studies to investigate variability of the ICG kinetics between different cases. In the simulations, we used a two-compartmental model to fit the physiological parameters and analyzed the effects of limitations of the DOT in the calculation of these parameters. We calculated ICG curves by varying the size of the imaging region, the size and the location of the inclusion. Although the ICG kinetics were same for all of them, the recovered kinetics were different in each case. Especially, when the structural priors were not used in the calculation of optical parameters, the calculated K^{trans} , k_{ep} , and v_p values had large variations among different cases. As a result, time to reach the peak ICG concentration showed significant variations within different cases. However, when the structural *a priori* was used, these variations were reduced. Consequently, when the ICG curves were normalized with respect to their maximum values, they overlaid on top of each other. In other words, although the recovered peak concentration was still case dependent (this is why a normalization was needed), the variability of the shape of the kinetic curve was reduced between different cases when *a priori* information was used in the reconstruction. The rising and the descending slope of the curves showed minimal variability. Therefore, we showed that the peak concentration was not an informative parameter when it was used to make comparisons between different cases. This was previously mentioned by Alacam *et al* 2006a.

In fact, it is seen from the structure of the equation (4) that the rate constant, k_{ep} , is more related to the rising and the descending slopes of the kinetic curve whereas K^{trans} is more affected by the peak value since it appears as an amplitude factor in the triple exponential function. Therefore, especially the accuracy of the recovered K^{trans} is limited by the spatial resolution and depth penetration of the DOT. Proper normalization can reduce the variations in k_{ep} in difference cases since it appears as slope. However, due ill-posedness of inverse DOT problem, k_{ep} is sensitive to random noise such as shot noise coming from the instrumentation. Although baseline correction can get rid of the systematic noise in each time point, it would not correct the errors coming from the random noise at each time point. The reason is that the random noise at each time point may not be the same. As a result, even in difference imaging there

would be some noise that is not possible to correct. In this manuscript, we show that the random noise could cause variations in the recovered ICG kinetics in imaging of small objects in large volumes.

The analysis presented in this study shows that the ICG kinetics curves obtained by a frequency domain DOT system have the potential for tumor characterization as long as the limitations of the optical imaging of deep tissue are taken into account. The anatomical information obtained from MRI can be used to improve the accuracy of the physiologically relevant parameters calculated from the enhancement kinetics of the ICG.

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Figure 1.

(a) Simulation geometry. (b) The true ICG kinetics in the simulations, and (c) the corresponding μ_a change in the ROI. 20 time points were simulated in the study.

Figure 2.

Reconstructed optical parameters for baseline **simulations** for the case (80,15,25). First row shows the true optical parameter distributions, second row shows the reconstruction without *a priori* knowledge, and the third row shows the reconstruction with *a priori* knowledge of the location of the inclusion.

Figure 3. Reconstructed optical parameter at three time points for the case (80,15,25). First row shows the reconstructions without using *a priori* knowledge and the second row shows the reconstructions using *a priori* knowledge of the location of the inclusion.

Figure 4.

Comparison of ICG and normalized ICG curves in two circular regions. i.e. (100,15,25) denotes a 100-*mm*-diameter circular region with a 15-*mm*-diameter target located 25 *mm* away from the center. First row: No structural priors were used in the calculation of optical parameters, and as a result the calculated ICG kinetics had gross errors. Second row: Structural priors were used. The shape of the ICG kinetics was recovered accurately.

Table 1

The percentage error in the peak ICG concentration in each case. It is important to note that the ICG kinetics for the 8-*mm* inclusion was recovered with the largest error.

Case	Error in peak ICG	
	Without <i>a priori</i>	With <i>a priori</i>
(100,15,0)	74%	6 %
(100,8,25)	84%	39%
(100,15,25)	72%	9%
(80,15,0)	58%	1%
(80,15,25)	66%	6%
(80,8,25)	78%	31%

Table 2

The calculated physiological parameters and their variability. In the DOT reconstruction *a priori* information was not used.

Case	K^{Trans} (sec^{-1})	k_{ep} (sec^{-1})	v_p
True value	0.0058	0.026	0.0142
(100,15,0)	0.0008	0.0118	0.0110
(100,8,25)	0.0022	0.0112	0.0090
(100,15,25)	0.0009	0.0125	0.0114
(80,15,0)	0.0032	0.0357	0.0001
(80,15,25)	0.0009	0.0147	0.0436
(80,8,25)	0.0030	0.0793	0.0060
Mean	0.0018	0.0442	0.0135
Standard deviation	0.0011	0.0418	0.0153
Coefficient of variation	60%	95%	114%

Table 3

The calculated physiological parameters and their variability. *A priori* information was used in the DOT reconstruction.

Case	K^{Trans} (sec^{-1})	k_{ep} (sec^{-1})	v_p
True value	0.0058	0.026	0.0142
(100,15,0)	0.0058	0.0242	0.0158
(100,8,25)	0.0025	0.0158	0.0082
(100,15,25)	0.0044	0.0201	0.0109
(80,15,0)	0.0045	0.0203	0.0382
(80,15,25)	0.0044	0.0182	0.002
(80,8,25)	0.0031	0.0179	0.0099
Mean	0.0041	0.0194	0.0139
Standard deviation	0.0012	0.0029	0.0130
Coefficient of variation	29%	15%	93%