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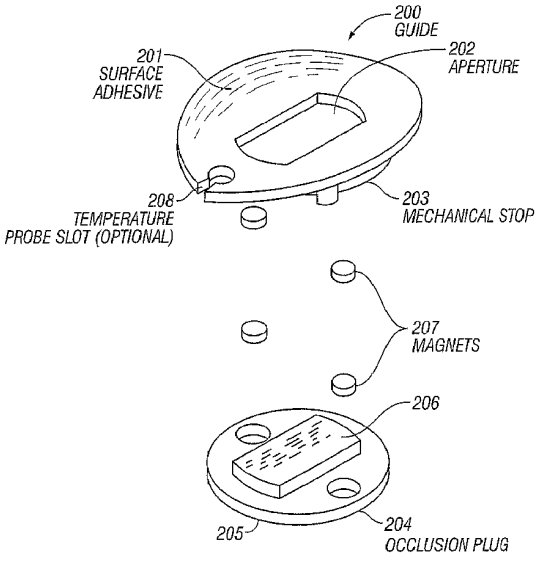
(54) Title: OPTICAL SAMPLING INTERFACE SYSTEM FOR *IN-VIVO* MEASUREMENT OF TISSUE



(57) Abstract: An optical sampling interface system is disclosed that minimizes and compensates for errors that result from sampling variations and measurement site state fluctuations. Embodiments of the invention use a guide that does at least one of, induce the formation of a tissue meniscus, minimize interference due to surface irregularities, control variation in the volume of tissue sampled, use a two-part guide system, use a guide that controls rotation of a sample probe and allows z-axis movement of the probe, use a separate base module and sample module in conjunction with a guide, and use a guide that controls rotation. Optional components include an occlusive element and a coupling fluid.

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OPTICAL SAMPLING INTERFACE SYSTEM FOR *IN-VIVO* MEASUREMENT OF TISSUE

BACKGROUND OF THE INVENTION

TECHNICAL FIELD

The invention relates to optical sampling of tissue *in-vivo*. More particularly, the invention relates to an optical sampling interface system that includes an optical probe placement guide, a means for stabilizing the sampled tissue, an optical coupler for repeatably sampling a tissue measurement site *in-vivo*, and/or a means for compensating for measurement bias.

DESCRIPTION OF THE PRIOR ART

In-vivo measurement of tissue properties and analytes using optical based analyzers requires that a tissue measurement region be positioned and coupled with respect to an optical interface or probe. The requirements of an optical sampling interface system for such placement and coupling depends upon the nature of the tissue properties and analytes under consideration, the optical technology being applied, and the variability of the tissue with respect to the target analyte. Often, when sampling reproducibility is vital, the optical measurement is performed in a laboratory where the majority of the factors pertaining to the measurement are controlled or constrained. However, there are many demanding *in-vivo* applications that cannot be performed in a laboratory setting, but yet require a high degree of optical sampling

reproducibility. In one example, a relatively unskilled operator or user must perform the optical measurement. One such application is the noninvasive estimation of glucose concentration through near-infrared spectroscopy. With the desired end result being an optical measurement system that is used by the consumer in a variety of environments, the optical sampling requirements are stringent. This problem is further considered through a discussion of the target application, the structure of live skin, and the dynamic properties of live tissue.

DIABETES

Diabetes is a chronic disease that results in abnormal production and use of insulin, a hormone that facilitates glucose uptake into cells. While a precise cause of diabetes is unknown, genetic factors, environmental factors, and obesity play roles. Diabetics have increased risk in three broad categories: cardiovascular heart disease, retinopathy, and neuropathy. Diabetics often have one or more of the following complications: heart disease and stroke, high blood pressure, kidney disease, neuropathy (nerve disease and amputations), retinopathy, diabetic ketoacidosis, skin conditions, gum disease, impotence, and fetal complications. Diabetes is a leading cause of death and disability worldwide. Moreover, diabetes is merely one among a group of disorders of glucose metabolism that also includes impaired glucose tolerance and hyperinsulinemia, which is also known as hypoglycemia.

DIABETES PREVALENCE AND TRENDS

The prevalence of individuals with diabetes is increasing with time. The World Health Organization (WHO) estimates that diabetes currently afflicts 154 million people worldwide. There are 54 million people with diabetes living in developed countries. The WHO estimates that the number of people with diabetes will grow to 300 million by the year 2025. In the United States, 15.7 million people or 5.9 percent of the population are estimated to have diabetes. Within the United States, the prevalence of adults diagnosed with diabetes increased by 6% in 1999 and rose by 33% between 1990 and 1998. This corresponds to approximately eight hundred thousand new cases every year in America. The estimated total cost to the United States economy alone exceeds $90 billion per year. Diabetes Statistics, National Institutes of Health, Publication No. 98-3926, Bethesda, MD (November 1997).

NONINVASIVE ESTIMATION OF GLUCOSE CONCENTRATION

Numerous approaches have been explored for estimating blood glucose concentrations, ranging from invasive methods such as microdialysis to noninvasive technologies that rely on spectroscopy. Each method has associated advantages and disadvantages, but only a few have received approval from certifying agencies. To date, no noninvasive techniques for the self-monitoring of blood glucose concentration have been certified by the U.S. Food and Drug Administration.

One method, near-infrared spectroscopy, involves the illumination of a region of the body with near-infrared electromagnetic radiation, *i.e.* light in the

wavelength range 700 to 2500 nm. The light is partially absorbed and scattered, according to its interaction with the tissue constituents prior to being reflected back to a detector. The detected light contains quantitative information that is based on the known interaction of the incident light with components of the body tissue including water, fat, protein, and glucose.

Previously reported methods for the noninvasive estimation of glucose concentration through near-infrared spectroscopy rely on the detection of the magnitude of light attenuation caused by the absorption signature of blood glucose as represented in the targeted tissue volume. The targeted tissue volume is that portion of irradiated tissue from which light is reflected or transmitted to the spectrometer detection system. The signal due to the absorption of glucose is extracted from the spectral measurement through various methods of signal processing and one or more mathematical models. The models are developed through the process of calibration on the basis of an exemplary set of spectral measurements and associated reference blood glucose concentrations (the calibration set) based on an analysis of capillary (fingertip) blood, venous blood, and/or alternative site fluids.

Near-infrared spectroscopy has been demonstrated in specific studies to represent a possible approach for the noninvasive measurement of blood glucose levels. M. Robinson, R. Eaton, D. Haaland, G. Keep, E. Thomas, B. Stalled, P. Robinson, *Noninvasive glucose monitoring in diabetic patients: A preliminary evaluation*, Clin Chem, 38:1618-22 (1992) reports three different

instrument configurations for measuring diffuse transmittance through the finger in the 600-1300 nm range. Meal tolerance tests were used to perturb the glucose concentrations of three subjects and calibration models were constructed specific to each subject on single days and tested through cross-validation. Absolute average prediction errors ranged from 19.8 to 37.8 mg/dL. H. Heise, R. Marbach, T. Koschinsky, F. Gries, Noninvasive *blood glucose sensors based on near-infrared spectroscopy*, Artif Org, 18:439-47 (1994); H. Heise, R. Marbach, *Effect of data pretreatment on the noninvasive blood glucose measurement by diffuse reflectance near-IR spectroscopy*, SPIE Proc, 2089:114-5 (1994); R. Marbach, T. Koschinsky, F. Gries, H. Heise, Noninvasive *glucose assay by near-infrared diffuse reflectance spectroscopy of the human inner lip*, Appl Spectrosc, 47:875-81 (1993); and R. Marbach, H. Heise, *Optical diffuse reflectance accessory for measurements of skin tissue by near-infrared spectroscopy*, Applied Optics 34(4):610-21 (1995) present results through a diffuse reflectance measurement of the oral mucosa in the 1111 to 1835 nm range with an optimized diffuse reflectance accessory. *In-vivo* experiments were conducted on single diabetics using glucose tolerance tests and on a population of 133 different subjects. The best standard error of estimation reported was 43 mg/dL and was obtained from a two-day single person oral glucose tolerance test that was evaluated through cross-validation.

K. Jagemann, C. Fischbacker, K. Danzer, U. Muller, B. Mertes, *Application of near-infrared spectroscopy for noninvasive determination of blood/tissue glucose using neural network*, Z Phys Chem, 191S: 179-190 (1995); C.

Fischbacker, K. Jagemann, K. Danzer, U. Muller, L. Papenkrodt, J. Schuler, *Enhancing calibration models for noninvasive near-infrared spectroscopic blood* glucose determinations, Fresenius J Anal Chem 359:78-82 (1997); K. Danzer, C. Fischbacker, K. Jagemann, K. Reichelt, *Near-infrared diffuse reflection spectroscopy for noninvasive blood-glucose monitoring,* LEOS Newsletter 12(2):9-11 (1998); and U. Muller, B. Mertes, C. Fischbacker, K. Jagemann, K. Danzer, *Noninvasive blood glucose monitoring by means of new infrared spectroscopic methods for improving the reliability of the calibration models*, Int J Artif Organs, 20:285-290 (1997) recorded spectra in diffuse reflectance over the 800 to 1350 nm range on the middle finger of the right hand with a fiber-optic probe. Each experiment involved a diabetic subject and was conducted over a single day with perturbation of blood glucose concentrations through carbohydrate loading. Results, using both partial least squares regression and radial basis function neural networks, were evaluated on single subjects over single days through cross-validation. Danzer, *et al., supra*, report an average root mean square measurement error of 36 mg/dL through cross-validation over 31 glucose concentration profiles.

J. Burmeister, M. Arnold, G. Small, *Human noninvasive measurement of glucose using near infrared spectroscopy* [abstract], Pittcon, New Orleans LA (1998) collected absorbance spectra through a transmission measurement of the tongue in the 1429 to 2000 nm range. A study of five diabetic subjects was conducted over a 39-day period with five samples taken per day. Every fifth sample was used for an independent test set and the standard error of estimation for all subjects was greater than 54 mg/dL.

T. Blank, T. Ruchti, S. Malin, S. Monfre, *The use of near-infrared diffuse reflectance for the noninvasive prediction of blood glucose*, IEEE Lasers and Electro-Optics Society Newsletter, 13:5 (October 1999), report studies that demonstrate noninvasive estimation of blood glucose concentration during modified oral glucose tolerance tests over a short time period. The calibration was customized for the individual and tested over a relatively short time period.

In all of these studies, diverse limitations were cited that affect the acceptance of such a method as a commercial product. Fundamental to all the studies is the problem of the small signal attributable to glucose, particularly in view of the difficulty in obtaining a reproducible sample of a given tissue volume, as a result of the complex and dynamic nature of the tissue. For example, see O. Khalil, *Spectroscopic and clinical aspects of noninvasive glucose measurements*, Clin Chem, v.45, pp.165-77 (1999). The sampling problem is further accentuated by noting that the reported studies were performed under highly controlled conditions using skilled professionals rather than in a home environment by the consumer. As reported by S. Malin, T. Ruchti, *An Intelligent System for Noninvasive Blood Analyte Prediction,* U.S. Patent No. 6,280,381 (August 28, 2001), the entirety of which is hereby incorporated by reference, chemical, structural and physiological variations occur that produce dramatic and nonlinear changes in the optical properties of the tissue sample. See R. Anderson, J. Parrish, *The optics of human skin*, Journal of Investigative Dermatology, 7:1, pp.13-19 (1981); W.

Cheong, S. Prahl, A. Welch, *A review of the optical properties of biological tissues*, IEEE Journal of Quantum Electronics, 26:12, pp.2166-2185, (December 1990); D. Benaron, D. Ho, *Imaging (NIRI) and quantitation (NIRS) in tissue using time-resolved spectrophotometry: the impact of statically and dynamically variable optical path lengths*, SPIE, 1888, pp.10-21 (1993); J. Conway, K. Norris, C. Bodwell, *A new approach for the estimation of body composition: infrared interactance*, The American Journal of Clinical Nutrition, 40, pp.1123-1140 (December 1984); S. Homma, T. Fukunaga, A. Kagaya, *Influence of adipose tissue thickness in near infrared spectroscopic signals in the measurement of human muscle*, Journal of Biomedical Optics, 1:4, pp.418-424 (October 1996); A. Profio, *Light transport in tissue*, Applied Optics, 28:12), pp. 2216-2222, (June 1989), M. Van Gemert, S. Jacques, H. Sterenborg, W. Star, *Skin optics*, IEEE Transactions on Biomedical Engineering, 36:12, pp.1146-1154 (December 1989); and B. Wilson, S. Jacques, *Optical reflectance and transmittance of tissues: principles and applications*, IEEE Journal of Quantum Electronics, 26:12, pp. 2186-2199.

The measurement is further complicated by the heterogeneity of the sample, the multi-layered structure of the skin, the rapid variation related to hydration levels, changes in the volume fraction of blood in the tissue, hormonal stimulation, temperature fluctuations, and changes in blood constituent concentrations. This is further considered through a discussion of the scattering properties of skin and the dynamic nature of the tissue.

专利名称(译)	用于组织体内测量的光学采样接口系统		
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摘要(译)

公开了一种光学采样接口系统，其最小化并补偿由采样变化和测量位置状态波动引起的误差。本发明的实施例使用引导至少一个，引起组织弯月面的形成，最小化由于表面不规则引起的干扰，控制采样的组织体积的变化，使用两部分引导系统，使用指南，控制样品探针的旋转并允许探针的z轴移动，使用单独的基础模块和样品模块与指南一起使用，并使用控制旋转的指南。可选组件包括闭塞元件和耦合流体。