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(54)【発明の名称】ＮＩＲベース血液検体判定中のスペクトル効果の最小化

(57)【要約】
【課題】組織状態の変動により発生する非侵襲性ｉｎ－ｖｉｖｏスペクトル測定における交絡効果を最小化する方法及び装置を提供すること。
【解決手段】組織状態の変動により発生する非侵襲性ｉｎ－ｖｉｖｏスペクトル測定における交絡効果を最小化する方法及び装置は、選択したパラメータにおける変化に起因するスペクトル効果が最小化されるターゲット範囲内で、選択した組織状態パラメータをモニタする。本発明は、選択した組織状態パラメータをターゲット範囲内に維持する能動的制御手段と受動的制御手段とを含む。

【特許請求の範囲】
【請求項１】
ＮＩＲベースの非侵襲性血液検体判定中に組織状態較差に起因するスペクトル効果を制御する方法であって、
選択した組織状態パラメータに関する値のターゲット範囲を決定するステップと、
当該組織状態パラメータを修正する手段を提供するステップと、
当該スペクトル効果を当該組織状態パラメータにおける較差に相関させるキャリブレーションモデルを提供するステップと、
ＮＩＲスペクトルを測定し、当該キャリブレーションモデルに従って当該スペクトルから当該パラメータに関する値を計算することにより、当該組織状態パラメータをモニタするステップと、
当該計算値が当該ターゲット範囲外である場合に、当該パラメータに関する測定値が当該ターゲット範囲内になるまで、当該組織状態パラメータを修正するステップと、
を含む方法。
【請求項２】
当該組織状態パラメータが、生きている被験者の身体の一部の組織測定部位の近隣における皮膚温度を含む、請求項１の方法。
【請求項３】
当該スペクトル効果が、ＮＩＲスペクトルにおけるピーク水吸収帯域のシフトを含み、当該ピーク水吸収帯域が、皮膚温度の上昇と共に短波長へシフトし、当該ピーク水吸収帯域が、皮膚温度の低下と共に長波長へシフトし、
当該シフトにより最終的な検体信号が減衰する、請求項２の方法。
【請求項４】
当該水吸収帯域が、約１４５０ｎｍの波長領域において発生する、請求項３の方法。
【請求項５】
当該シフトが最小化され、当該最終的な検体信号の当該減衰が最小化されるような皮膚温度の範囲を、当該ターゲット範囲が有する、請求項３の方法。
【請求項６】
当該ターゲット範囲が、およそ華氏８９～９１度である、請求項５の方法。
【請求項７】
ターゲット範囲を決定する当該ステップが、
当該シフトが最小化される温度範囲を決定するためにキャリブレーションデータからのスペクトルを調査することにより当該ターゲット範囲を経験的に決定するステップを含む、請求項３の方法。
【請求項８】
組織状態パラメータを修正する当該手段が、
当該皮膚温度を能動的に制御する手段と、
当該皮膚温度を受動的に制御する手段との一方又は両方を含む、請求項２の方法。
【請求項９】
当該能動的手段及び当該受動的手段が、皮膚を当該ターゲット範囲に維持するために相補的な形で利用される、請求項８の方法。
【請求項１０】
当該能動的制御手段が、皮膚温度の急激な変化を引き起こすために利用される、請求項９の方法。
【請求項１１】
当該受動的制御手段が、比較的長い期間に渡って利用される、請求項８の方法。
【請求項１２】
当該皮膚温度を受動的に制御する当該手段が、当該身体の一部に適用する熱ラップを含み、当該熱ラップの最初の適用により皮膚温度が上昇する、請求項８の方法。
【請求項１３】

皮膚温度が、当該熱ラップを緩めるステップと、締め付けるステップと、取り去るステップとのいずれかにより、当該ターゲット範囲内に維持される、請求項１２の方法。
【請求項１４】
当該皮膚温度を能動的に制御する当該手段が、温度制御ヒートシンクを含む、請求項８の方法。
【請求項１５】
当該ヒートシンクが、当該ターゲット範囲内の設定値を有し、皮膚温度を当該ターゲット範囲内に維持するために、当該ヒートシンクが当該皮膚を冷やすまたは暖める、請求項１４の方法。
【請求項１６】
能動的制御が、当該ヒートシンクと接触する皮膚に局所化される、請求項１４の方法。
【請求項１７】
当該キャリブレーションモデルを提供する当該ステップが、関連する皮膚温度基準測定値と組み合わせた例示的な被験者のグループに関するスペクトル測定値を含むキャリブレーションデータセットを使用して当該キャリブレーションモデルを作成するステップを含む、請求項３の方法。
【請求項１８】
当該基準測定値が、当該ターゲット範囲とほぼ等しい範囲、またはこれより広い範囲に及ぶ、請求項１７の方法。
【請求項１９】
当該基準測定値が、組織測定部位の間近に配置された非侵襲性温度センサを使用して作成される、請求項１７の方法。
【請求項２０】
当該キャリブレーションが、多変量分析手法を使用して作成され、当該モデルが、当該シフト情報を多変量回帰係数に黙示的に取り入れる、請求項１７の方法。
【請求項２１】
当該組織状態パラメータをモニタする当該ステップが、ステップとして、
当該ＮＩＲスペクトルから吸収スペクトルを計算するステップと、
随意的に、当該吸収スペクトルを前処理するステップと、
当該多変量キャリブレーションモデルを適用することにより皮膚温度を計算するステップとを含む、請求項２０の方法。
【請求項２２】
当該組織状態パラメータを修正する当該ステップが、皮膚温度が当該ターゲット範囲へ戻るように当該制御手段を適用するステップを含む、請求項２１の方法。
【請求項２３】
ＮＩＲベースの非侵襲性血液検体判定中に組織状態較差に起因するスペクトル効果を制御する装置であって、
選択した組織状態パラメータを修正する手段と、
組織測定部位でＮＩＲスペクトルを測定する手段と、
当該スペクトル効果を当該組織状態パラメータにおける較差に相関させるキャリブレーションモデルと、
ＮＩＲスペクトルを測定し、当該キャリブレーションモデルに従って当該スペクトルから当該パラメータに関する値を計算することにより、当該組織状態パラメータをモニタする手段と、
を備え、
当該計算値がターゲット範囲外である場合に、当該パラメータが当該ターゲット範囲内になるまで、当該修正手段により当該組織状態パラメータを修正する装置。
【請求項２４】
当該組織状態パラメータが、生きている被験者の身体の一部の組織測定部位の近隣における皮膚温度を含む、請求項２３の装置。

【請求項２５】
当該スペクトル効果が、ＮＩＲスペクトルにおけるピーク水吸収帯域のシフトを含み、これにおいて、当該ピーク水吸収帯域が、皮膚温度の上昇と共に短波長へシフトし、当該ピーク水吸収帯域が、皮膚温度の低下と共に長波長へシフトし、
当該シフトにより最終的な検体信号が減衰する、請求項２４の装置。
【請求項２６】
当該水吸収帯域が、約１４５０ｎｍの波長領域において発生する、請求項２５の装置。
【請求項２７】
当該シフトが最小化され、当該最終的な検体信号の当該減衰が最小化されるような皮膚温度の範囲を、当該ターゲット範囲が有する、請求項２５の装置。
【請求項２８】
当該ターゲット範囲が、およそ華氏８９～９１度である、請求項２７の装置。
【請求項２９】
当該シフトが最小化される温度範囲を決定するためにキャリブレーションデータからのスペクトルを調査することによりターゲット範囲が経験的に決定される、請求項２５の装置。
【請求項３０】
組織状態パラメータを修正する当該手段が、
当該皮膚温度を能動的に制御する手段と、
当該皮膚温度を受動的に制御する手段との一方又は両方を含む、請求項２４の装置。
【請求項３１】
当該能動的手段及び当該受動的手段が、皮膚を当該ターゲット範囲に維持するために相補的な形で利用される、請求項３０の装置。
【請求項３２】
当該能動的制御手段が、皮膚温度の急激な変化を引き起こすために利用される、請求項３１の装置。
【請求項３３】
当該受動的制御手段が、比較的長い期間に渡って利用される、請求項３０の装置。
【請求項３４】
当該皮膚温度を受動的に制御する当該手段が、当該身体の一部に適用する熱ラップを含み、当該熱ラップの最初の適用により皮膚温度が上昇する、請求項３０の装置。
【請求項３５】
皮膚温度が、当該熱ラップを緩めるステップと、締め付けるステップと、除去するステップとのうちのいずれかのステップにより、当該ターゲット範囲内に維持される、請求項３４の装置。
【請求項３６】
ＮＩＲスペクトルを測定する当該手段が、ＮＩＲスペクトロメータ機器を含み、当該スペクトロメータ機器が、被験者インタフェースモジュールを含む、請求項３０の装置。
【請求項３７】
当該皮膚温度を能動的に制御する当該手段が、温度制御ヒートシンクを含む、請求項３６の方法。
【請求項３８】
当該ヒートシンクが、当該被験者インタフェースモジュールに組み込まれ、当該ヒートシンクが、使用中に当該組織測定部位と接触する、請求項３６の装置。
【請求項３９】
当該ヒートシンクが、当該ターゲット範囲内の設定値を有し、当該ヒートシンクが、皮膚温度を当該ターゲット範囲内に維持するために、当該皮膚を冷やすまたは暖める、請求項３７の装置。
【請求項４０】
能動的制御が、当該ヒートシンクと接触することになる皮膚に局所化される、請求項３７

の装置。
【請求項４１】
当該キャリブレーションモデルが、関連する皮膚温度基準測定値と組み合わせた例示的な被験者のグループに関するスペクトル測定値を含むキャリブレーションデータセットを使用して作成される、請求項２５の装置。
【請求項４２】
当該基準測定値が、当該ターゲット範囲とほぼ等しい範囲、またはこれより広い範囲に及ぶ、請求項４１の装置。
【請求項４３】
当該基準測定値が、組織測定部位の間近に配置された非侵襲性温度センサを使用して作成される、請求項４１の装置。
【請求項４４】
当該キャリブレーションが、多変量分析手法を使用して作成され、当該モデルが、当該シフト情報を多変量回帰係数に黙示的に取り入れる、請求項４１の装置。
【請求項４５】
当該組織状態パラメータが、
当該ＮＩＲスペクトルから吸収スペクトルを計算するステップと、
随意的に、当該吸収スペクトルを前処理するステップと、
当該多変量キャリブレーションモデルを適用することにより皮膚温度を計算するステップとによりモニタされる、請求項４４の装置。
【請求項４６】
当該組織状態パラメータが、皮膚温度が当該ターゲット範囲へ戻るように当該制御手段の一方又は両方を適用することにより修正される、請求項４４の装置。
【発明の詳細な説明】
【０００１】
【発明が属する技術分野】
本発明は、非侵襲性組織成分分析に関する。より詳しくは、本発明は、組織状態較差に起因する非侵襲性血液検体判定に関するＮＩＲスペクトル測定におけるスペクトル効果を最小化する方法及び装置に関する。
【０００２】
【従来の技術】
近赤外線（ＮＩＲ）組織分光法は、７００～２５００ナノメートル波長範囲のＮＩＲエネルギによる組織部位の照射に基づいた測定を行う将来性のある非侵襲性技術である。このエネルギは、皮膚の領域に集中させ、皮膚組織の散乱及び吸収特性に従って伝搬する。そのため、検出されるおよび検出されない反射又は伝達エネルギは、それが照射される皮膚体積に関する情報を提供する。具体的には、各波長での光エネルギの減衰は、組織の構造特性及び化学組成の関数となる。それぞれが異質な独自の粒子分布を含む組織層は、散乱により光吸収に影響する。水分、タンパク質、脂質、及び血液検体といった化学構成要素は、独自の吸収特性又はシグニチャにより、その濃度に比例して光を吸収する。組織特性、特徴、又は組成の測定は、それぞれの散乱及び／又は吸収特性の結果として生じる光減衰の大きさを検出することに基づく。
【０００３】
血糖濃度といった血液検体の非侵襲性予測はＮＩＲ分光法により行われてきたが、皮膚温度等の組織状態の変動は、最終的な検体信号の減少を発生させる可能性のあるスペクトル較差の増加をもたらす。これにより、貴重な検体情報の抽出が困難になる。
【０００４】
ヒト組織は、８０％程度の水を含む可能性があり、これはＮＩＲ吸収スペクトルにおいて、温度の関数である既知のピークシフトを有する。温度が上昇すると、水の帯域は、水素結合が減少する結果、短波長へシフトする。光は、組織に照射され、皮膚の層を通過し、皮膚の成分により吸収された後、皮膚から退出し、スペクトロメータにより検出される。

皮膚温度較差は、２種類の方法でスペクトル測定に持ち込まれる。第１に、結果として生じた信号は、ヒト組織の光学サンプリング経路に存在する自然温度勾配によるものを含め、通過した組織体積からのスペクトル情報を含んでいる。第２に、ヒト皮膚及び皮下組織では、環境及び生理的要素の結果として、均一な中心体温を維持するために、温度較差が生じる。健康な個人では、１日のうちに、皮膚温度が５°Ｆ程度変動することが観察されている。こうした要素により、データセットを含む測定結果の間で温度較差が生じる。そのため、データセットでは、測定中及び測定間に、水の帯域のシフトが存在することになる。データセットは、多変量数学的キャリブレーションモデルの作成により、対象の検体を推定するために使用される。

【０００５】

測定中及び測定間の温度較差により、多変量分析の複雑さのレベルは増加し、貴重な検体情報を抽出することは更に困難になる。温度の大きな較差は、最終的な検体信号を減少させる可能性のあるスペクトル較差の増加につながる。加えて、未制御の皮膚温度較差は、対象の検体と相関する可能性が高い。こうした偶発的相関は、誤ったキャリブレーションにつながる可能性があり、これは識別が可能な場合と不可能な場合とがある。

【０００６】

何らかの方法で試料温度をモニタ又は変更することを目的とした様々な分光学的方法及び装置が、従来技術で説明されている。例えば、Ｊ．ブレイグ、Ｄ．ゴールドバーガ、Ｂ．スターリングの米国特許第５，６１５，６７２号（１９９７年４月１日）「体温補正付き自己放射非侵襲性赤外線スペクトロメータ」では、血中のグルコースの赤外線放射を１０ミクロン近くの長い赤外線波長でモニタすることにより、被験者の血中のグルコース濃度を非侵襲的に測定する「自己放射」グルコースモニタについて説明している。説明されているデバイスは、ヒトの血液及び／又は周辺組織が放射する赤外線エネルギを利用し、吸収分析を実行する。成分濃度測定を温度依存効果に関して調整するために、ヒトの腕部の内部温度を測定する温度感知デバイスも使用される。体熱として放射されるヒト自身の赤外線エネルギを赤外線源として使用することにより、エネルギ源を供給する必要性は排除されるが、説明されているデバイス及び付随する方法では、個人の内部温度を決定する必要があり、しかしながら、このセンサは皮膚表面の温度を測定する。そのため、体内温度に関して計算した補正を測定スペクトル信号に適用することにより、検体濃度推定に大きな誤差のソースが持ち込まれる。加えて、このセンサの熱時定数により、望ましくない待ち時間が持ち込まれ、これは１．５分に及ぶ可能性がある。更に、説明されているデバイスは、単に、被験者の体温の影響を補正するスペクトル信号に対する修正を計算するに過ぎない。温度に関連するスペクトル効果を最小化する最適な試料温度を提供する目的でターゲット範囲内に温度を制御するための準備は存在しない。加えて、ブレイグらの教示内容は、中及び遠赤外線領域に関係している。

【０００７】

Ｍ．ブロックの米国特許第６，００２，９５３号（１９９９年１２月１４日）「鼓膜における検体の非侵襲性ＩＲ伝達測定」では、選択した血液成分の濃度を測定する非侵襲性方法及び装置を説明している。これにおいては、光学デバイスを外耳道に挿入し、電磁放射の一部をＩＲ検出及び分析デバイスに向けている。鼓膜は、内耳との温度差動を形成するために冷却され、これにより鼓膜全体での熱放射の放出が促進される。光学機器を耳道に深く挿入すること及び鼓膜を冷却することは、決して侵襲的ではないが、静脈穿刺等の外傷性の方法と比較すると低侵襲性であると考えられる場合がある。ブロックの教示内容において、測定部位の温度の分光法ベースの測定は準備されていない。鼓膜の冷却は、組織状態の変動のスペクトル効果を最小化するためではなく、熱伝達を促進するために行われる。型通りの方法で鼓膜を冷却することを除き、ブロックのデバイスは、測定部位の温度を制御することができない。ブロックのデバイスは、更に、分光学的温度判定により部位温度の制御に必要なフィードバックが提供される閉ループを提供しない。

【０００８】

Ｊ．ブレイグ、Ｃ．クレイマ、Ｂ．スターリング、Ｄ．ゴールドバーガ、Ｐ．ジェン、Ａ

．シュレンバーガ、Ｒ．トレビノ、Ｒ．キング、Ｃ．バーンズの米国特許第６，１６１，０２８号（２０００年１２月１２日）「周期的温度変調及び位相検出を使用して検体濃度を判定する方法」では、ブロックのものと同様の理論を利用したテスト試料の検体濃度を判定する方法を説明している。テスト試料に温度勾配を導入し、赤外線放射検出器が、選択した検体の吸収ピーク及び基準波長での放射を測定する。ブレイグらの教示内容では、勾配分光法が利用され、熱伝達を促進するために、試料において熱勾配が生成され、これにより、更に多くの熱放射が放射検出器に伝達される。説明されている方法は、測定部位での組織状態の変動に関連するスペクトル効果と、これによる最終的な検体信号に対する交絡効果との問題は解決していない。この説明されている方法では、試料において温度勾配を誘導することを除き、試料温度の変動により生じるスペクトル効果を最小化するターゲット範囲内に試料温度を制御する方法は、提供されていない。

【０００９】

従来技術により解決されていない問題点について考えると、ＮＩＲベースの非侵襲性血液検体判定中に、皮膚温度等の組織状態較差に起因するスペクトル効果を制御する方法に関する必要性が存在する。これは、選択した組織状態パラメータをモニタし、こうしたスペクトル効果が最小化される既定のターゲット範囲の値にこれを維持することにより行われる。組織状態パラメータを分光学的にモニタすることは、技術的に大きな利点である。これにおいて、キャリブレーションモデルは、選択した組織状態パラメータのシフトを観察されたスペクトル効果のシフトに相関させることにより測定値を計算し、これにより従来のセンサデバイスには必要であった時定数が不必要になる。計算値が、適用する制御の度合いを決定するためのフィードバックを提供する、閉ループにより駆動される、選択した組織状態パラメータを制御する手段が、提供されることが、好ましい。

【００１０】

【課題を解決するための手段】

本発明は、組織状態の変動により発生する非侵襲性ｉｎ－ｖｉｖｏスペクトル測定における交絡効果を最小化する方法及び装置を提供する。選択した組織状態パラメータは、分光学的変化を選択組織状態パラメータの変動に相関させる多変量キャリブレーションモデルの適用により、分光学的にモニタされ、ほぼ瞬間的な測定値が提供され、任意の大きな時定数が強制されることはない。選択したパラメータのターゲット範囲の値は、選択したパラメータの変化に起因するスペクトル効果が最小化される値の範囲を決定するためにデータセットのスペクトルを観察することにより、実験データセットから経験的に決定される。測定中、選択したパラメータは、継続的にモニタされる。計算値は、選択した組織状態パラメータをターゲット範囲内に維持するデバイスを駆動する閉ループにフィードバックを提供する。組織状態パラメータの能動的及び受動的制御の両方に関する手段が、本発明に含まれる。

【００１１】

本発明の好適な実施形態は、組織測定部位での皮膚温度のシフトに起因する非侵襲性近赤外線スペクトル測定における交絡効果を最小化する方法及び装置を提供する。測定部位の皮膚温度は、分光学的変化を皮膚温度のシフトに相関させる多変量キャリブレーションモデルの適用により温度値を計算することにより、分光学的にモニタされる。従来の温度感知デバイスにより強制される熱時定数は、排除され、ほぼ瞬間的な温度表示値が提供される。能動的及び受動的制御手段が提供される。受動的制御は、閉塞性熱ラップの選択的な適用及び除去により達成される。能動的制御は、測定部位の近隣の皮膚に適用したサーミスタにより提供される。能動的及び受動的制御は、相補的な形で適用することが可能であり、または、別個に使用することができる。本発明の特に好適な実施形態において、制御手段は、測定機器に組み込まれ、計算された皮膚温度値は、制御デバイスを駆動する閉ループにおいてフィードバックを提供する。本発明の代替実施形態において、この温度値は、操作者に供給され、その後、この操作者は、皮膚温度をターゲット範囲に入れて、これを維持するために、能動的及び／又は受動的制御を適用する。皮膚温度を分光学的にモニタすることと、受動的及び／又は能動的制御の方法を利用することとにより、ＮＩＲ測定

に対する皮膚温度の影響を低減することが可能となる。本発明は、血糖濃度の非侵襲性測定において独自の応用が可能である。

【００１２】

【発明を実施するための形態】

ＮＩＲ分光法を使用した皮膚温度測定及び制御

関連する皮膚温度基準測定と組み合わせた皮膚の近赤外線測定は、皮膚表面温度の予測にＮＩＲ組織スキャンしか必要としないＮＩＲ温度キャリブレーションを作成するために使用される。スペクトル分析に関するキャリブレーションを作成する方法では、当業者に広く知られている様々な多変量分析手法を利用することができる。ＮＩＲ皮膚温度キャリブレーションは、皮膚温度における較差による１４５０ｎｍの水の帯域の既知のシフティングにより可能となる。このキャリブレーションモデルは、シフト情報を多変量回帰係数に黙示的に取り入れる。ヒト組織の温度の測定及び制御は、検体信号の抽出を妨げる複合重複スペクトル効果を簡略化する手段を提供するため、非侵襲性ＮＩＲ測定において重要である。付加的な温度測定ハードウェアと、関連するコスト及び複雑性とは、ＮＩＲ温度測定を使用することにより回避される。

【００１３】

一次サーミスタ測定と比較したＮＩＲ測定の利点は、従来の感知ハードウェアに内在する熱時定数の欠如にある。測定された皮膚サーミスタ反応では、１０°Ｆの段階変化の下で試料温度変化の９５％を反映するために、１．５分程度を要することが頻繁にある。温度測定の時定数を排除することは、一次測定方法に内在する時定数に妨げられない、ほぼ瞬間的な皮膚温度フィードバックを提供することにより、皮膚の能動的閉ループ温度制御の実施に大きな利点を提供する。

【００１４】

多数の個体に関する皮膚温度キャリブレーションは、単一の被験者からのキャリブレーションデータを使用して達成される。この結果、機器の出荷前に現場で確立できる一般的な皮膚温度キャリブレーションの実現可能性が予言される。

【００１５】

皮膚温度の能動的及び受動的制御の手順は、下に提示されている。近赤外線（ＮＩＲ）組織分光法は、皮膚を照射し、ヒト被験者の生物学的検体を推定するために利用される。皮膚温度較差は、２種類の形でＮＩＲ測定にとって有害である。第１に、皮膚温度が対象の検体と相関する場合に誤ったキャリブレーションが発生する可能性があり、第２に、大きな皮膚温度の変動は最終的な検体信号を減少させる。最終的な検体信号を減らすことと、偽の相関とを防止するために、皮膚温度を受動的及び能動的に制御する装置及び手順について説明する。この皮膚温度を制御する方法には、ターゲット皮膚温度を決定することと、実際の皮膚温度をモニタすることと、ターゲット温度を達成するために受動的及び／又は能動的制御方法を適用することとが関与する。

【００１６】

実験は、以下の目的で実施される。

・ＮＩＲ測定に対する皮膚温度較差の影響を特徴付ける－下の実験Ｉ及びＩＩを参照されたい。

・１日及び数日間の皮膚温度プロフィールを特徴付ける－下の実験ＩＩ及びＩＩＩを参照されたい。

・皮膚温度を±１°Ｆ内で制御する方法をテストする－下の実験ＩＩＩを参照されたい。

【００１７】

皮膚温度制御の方法

皮膚の主要な機能の一つは、一定の体温を維持することである。外的及び内的刺激に対する生理的反応は、皮膚温度の制御を制限する可能性がある。周期的モニタリングは、優れた温度制御を達成する上で重要なステップである。本発明を使用することにより、当業者は、皮膚温度の傾向を見極め、補正として受動的及び／又は能動的制御を実施し、これにより、スペクトル測定部位において安定した皮膚温度が維持される。

【００１８】
皮膚温度は、スペクトル測定部位から５ｍｍ以内の皮膚に取り付けた温度プローブを使用してモニタされる。下に示す実験ＩＩの説明のように、毎日の皮膚温度プロフィールは、一般に温度が朝に低く、日中、徐々に上昇することを示しており、結果として、プロフィールは、時間と共に安定する緩やかな正の傾斜を有する。下の実験ＩＩＩの説明において指摘するように、健康な場合及び糖尿病の場合の皮膚温度プロフィールでは、初期ターゲット皮膚温度の範囲が９０～９２°Ｆとなり、これは昼下がりから夕方に観察される温度の代表値である。ターゲット範囲は、個人により変化する。以下の方法は、ターゲット範囲を達成及び維持するために利用される。

【００１９】
受動的制御
被験者の前腕部に巻いた熱ラップを用いた受動的制御は、午前中に皮膚温度を素早くターゲット温度にするために実施することができる。これにより、最初の１時間に急勾配の正の傾斜を有するプロフィールが生じ、その後、その日のそれ以後の間に、皮膚温度はより均一になる。このラップは、手首から肘の前腕部を覆うため、前腕部全体の温度が上昇する。このラップは、被験者の腕部で、緩くなるように、又はきつくなるように、調整することが可能であり、または、皮膚温度をターゲット範囲に維持するために、必要に応じて取り外すことができる。

【００２０】
能動的制御
能動的制御では、皮膚の温度を迅速に変化させる温度制御式銅製ヒートシンクを利用することができる。このヒートシンクの設定値は、皮膚を暖めるため又は冷やすために、調整することができる。能動的制御は、ヒートシンクと接触することになる皮膚に局所化され、この部分は被験者－スペクトロメータインタフェースと同じ寸法を有する。皮膚温度がスペクトル測定の直前にターゲット範囲から大きく外れている場合、測定前に腕部を１～２分間ヒートシンク上に置く。

【００２１】
上に提示した方法は、皮膚温度をターゲット範囲に維持するために、相補的な形で使用することができる。選択される方法は、スペクトル測定前に利用可能な時間と観察される皮膚温度との関数となる。能動的又は受動的制御を実施する判断は、皮膚温度がモニタされる度に、スペクトル測定前に利用可能な時間と、実際の温度及びターゲット温度の間の差異とに基づいて行う。受動的制御は、１～２分間より長い期間に最適であり、能動的制御は、温度を急激に上昇又は低下させる必要がある場合に有利である。皮膚温度を制御するための一般的な手順のフロー図は、図１４に提示されている。本明細書で説明されているように、ターゲット温度は、スペクトル測定値を観察し、スペクトル較差が最小に維持されるターゲット範囲を確立することにより、経験的に確立される（１４０）。ＮＩＲスペクトル測定値が収集され（１４１）、スペクトル効果を皮膚温度に相関させる多変量キャリブレーションをスペクトル測定値に適用することにより、皮膚温度が分光学的にモニタされる（１４２）。温度表示値が評価される（１４３）。皮膚温度がターゲット範囲内にある場合、制御は実施されない。皮膚温度がターゲット範囲外にある場合は、受動的（１４４）又は能動的（１４５）制御のいずれか、またはその組み合わせを実施し、温度をターゲット範囲に戻す。図１４及び１５から確認できるように、本発明のシステムは、閉ループを表し、これにおいて、制御デバイスは、分光学的温度判定により供給されるフィードバックにより駆動される。

【００２２】
本発明の方法を実施するスペクトロメータ機器は、図１５に表示されている。被験者インタフェースモジュール１５２は、被験者１５１の皮膚の組織測定部位に結合される。被験者インタフェースモジュール内にマウントされたサーミスタ１５９は、ターゲット範囲内の設定値を有する。設定値を維持するために、サーミスタは、皮膚表面を加熱又は冷却する。本発明の好適な実施形態において、被験者インタフェースモジュールは、光ファイバ

プローブを備える。被験者インタフェースモジュールは、光源１６０から放出された光を、組織測定部位に向けて送る。組織測定部位から逆拡散した光は、この例においては光ファイバである検出光学装置１５３により、１つ以上の光検出器１５４に向けて送られる。アナログ電子機器が、送られた光を電圧に変換し、これはその後、アナログ・デジタル変換器（ＡＤＣ）１５５によりデジタル値に変換される。このデジタル値から、吸収スペクトルが計算される１５６。この吸収スペクトルには、以前に説明した１つ以上の前処理手法１５７を施すことができる。その後、以前に説明したキャリブレーションモデルの適用により、吸収スペクトルから温度値が計算される１５８。最後に、計算温度値は、サーミスタ１５９とインタフェースするコントローラ（表示なし）に送られ、温度フィードバックが提供される。

【００２３】

実験Ｉ：ＮＩＲスペクトルに対する皮膚温度の影響

概要

ＮＩＲスペクトルの水の帯域に含まれる情報コンテンツに関して、アリゾナ州テンペのＩｎｓｔｒｕｍｅｎｔａｔｉｏｎ Ｍｅｔｒｉｃｓ，Ｉｎｃ．により供給されるＦＯＣＳＩ（光ファイバ結合スキャニング機器）スペクトロメータ機器の光学設定が、同じくＩｎｓｔｒｕｍｅｎｔａｔｉｏｎ Ｍｅｔｒｉｃｓ，Ｉｎｃ．により供給されるＤＲＡＣＯスペクトロメータ機器の光学設定より優れているかどうかを判断する目的で、予備研究を実施した。１４５０ｎｍの水の帯域は、試料温度によりシフトするので、広範な温度で採取された試料における水分及び組織中のグルコースのモデリングを困難にすることが知られている。そのため、血糖予測アルゴリズムは、モデリングの課題を簡略化するために、水の帯域におけるシフトを利用するキャリブレーション戦略を取り入れる必要がある。したがって、組織温度情報の評価を可能にする光学設計は、非侵襲性グルコースモニタに関して重要な設計基準である。この研究では、ＦＯＣＳＩ機器において様々な温度で取得した非侵襲性測定値が、ＤＲＡＣＯにおいて取得したものに比べ、予測されるスペクトル作用との一貫性が大幅に高いことが観察された。非侵襲性ＤＲＡＣＯ測定に内在する非常に変化しやすい試料パスレングスが、温度効果の解釈と混同したことが疑われる。

【００２４】

序論

ヒト組織には８０％程度の水が含まれているので、ＮＩＲ吸収スペクトルには、試料温度の上昇による既知のピークシフトが存在する。こうした短波長への水の帯域のシフトは、温度上昇による溶液のｐＨの上昇及び付随する水素結合の減少の結果として発生する。図１では、水の第１倍音帯の伝送スペクトルが、摂氏３３°（１１）及び４１°（１０）でプロットされている。ｉｎ－ｖｉｖｏ測定ピークには、ヒト組織の光学サンプリング経路に存在する自然温度勾配による温度状態の分布からのスペクトルの寄与が含まれることが予想できる。この熱複合試料マトリックスにおいてグルコースをモデル化することは、ＮＩＲ分光法を使用したｉｎ－ｖｉｖｏ測定の大きな課題の１つである。近赤外線による組織のプロービングは表面及び組織内での局所的な影響につながる可能性が高いため、組織温度の正確な補正は、スペクトル測定からの推論により取り組むのが最善である。測定を妨げることなく温度プローブをスペクトロメータの光経路に挿入することは不可能であり、非侵襲性温度プローブでは、組織内の温度勾配が明らかにならない。組織温度較差を補正する最も効果的な手段では、測定スペクトルが、水の帯域の位置及び形状に関する実体のある情報を含むことが必要となる。水の帯域の形状は、組織の光学特性にも影響され、情報性の高いスペクトルスキャンの取得は更に重要となる。こうした点を考慮すると、水の帯域の形状を歪ませる機器又は人工物は、極めて好ましくない。これは、ＮＩＲ分光法に基づく非侵襲性グルコース計測器の設計に強く影響することになる。

【００２５】

実験

６人の被験者を、ＦＯＣＳＩ及びＤＲＡＣＯスキャニングスペクトロメータの両方でスキャンした。各被験者について、２セットの実験を実施した。第１の実験では、被験者を通

常の周囲皮膚温度でスキャンし、第２の実験では、被験者の皮膚温度を通常の皮膚温度より３～５°Ｆ高くなるように事前に加熱した後で実施した。この研究の前に取得した測定値から、スペクトル測定に関する以下のプロトコルが確立された：急激な温度及び生理的変化は、スペクトルの取得前に機器－被験者インタフェースモジュールに腕部を３分間接触させることにより低減させた。実験中には、オハイオ州イエロースプリングのＹＳＩ，Ｉｎｃ．が供給するＹＳＩ４０００皮膚温度センサを、±０．０５°Ｆの表示値で、測定部位から約５ｍｍに配置した。温度は、３０秒毎に記録し、スキャンは２分間に渡って実施した。８０％の反射率標準を使用した基準スペクトルは、ｉｎ－ｖｉｖｏ測定の直前及び直後に取得した。

【００２６】

結果及び説明

各スペクトロメータ機器で取得したスキャン結果は、６人の被験者のそれぞれに関して、温度関連効果について調査した。試料組織の温度分布と一致する温度関連効果は、ＦＯＣＳＩでスキャンした４人の残りの患者のうち３人で認められたが、ＤＲＡＣＯで取得されたスキャン結果において、温度関連効果は、これほど明白ではなかった。図２及び３では、２人の個人から２種類の温度レベルでＦＯＣＳＩにより取得されたスキャン結果が、プロットされている。一方のスペクトルのセットは、他方（２１、３１）よりも５°Ｆ高い皮膚温度で取得された（２１、３０）。高温でのスキャン結果において、１４５０ｎｍの最大吸収度と、１６５０～１７００ｎｍでの最小吸収度との間の強度の差異が大きいことは明白である。高温スペクトルピークのエッジは、更に、１４５０ｎｍの水の帯域の長波長側において、低温スペクトルの内部に存在する。こうしたスペクトルの差異は、加熱した組織における狭い範囲の水温の存在と一致して、鋭いピークを発生させる。散乱の理論によれば、組織の散乱は、温度と共に増加する。最も大きな散乱効果を有するスペクトル領域は、１１００～１３００ｎｍの第２倍音帯の周辺の短波長領域に存在する。散乱は、第２倍音領域を過ぎると急速に減少すると考えられている。温度の上昇による試料の吸収度の抑制は、予想される組織の光学的作用と一致する。温度による増加した散乱からの吸収度の減少は、第２倍音において目立つ。しかしながら、この減少は、水の帯域の最大値のような高い吸収スペクトル特徴の第１倍音においても著しい場合がある。

【００２７】

ＤＲＡＣＯで取得された対応するスキャン結果４０、５０、及び４１、５１は、図４及び５にプロットされている。以前に述べたように、温度効果は、図２及び３のスペクトルに比べて、まったく顕著ではない。冷却及び加熱した皮膚温度で取得された個別の被験者スペクトルを使用して計算された差スペクトルは、その組織における温度変化に関連するスペクトル情報を含むべきである。一貫性のある測定では、個別のテスト被験者それぞれに関して、類似する形状の差スペクトルが生じるべきである。冷却及び加熱した皮膚温度において各被験者で取得されたスペクトルを差し引き、結果として生じたＤＲＡＣＯスペクトロメータに関する差スペクトルが、図６にプロットされている。ＦＯＣＳＩ機器に関するものは、図７にプロットされている。明らかに、差スペクトル（冷却時から加熱時を減算）は、ＤＲＡＣＯにより取得された測定結果に比べ、ＦＯＣＳＩに関する形状において一貫性がある。第２倍音領域周辺での温度誘導散乱効果は、冷却スペクトルから加熱スペクトルを減算したものが高温の組織での散乱の増加から予想される正の残差を一貫して発生させる点において、ＦＯＣＳＩに関する散乱のリサーチと一致する。図６及び７から明白であるように、ＤＲＡＣＯ光学システムを使用した通常温度状態及び加熱温度状態での組織の測定結果の解釈は、ＦＯＣＳＩで取得された対応する測定結果のように簡単ではない。ＤＲＡＣＯ光学システムは、センサの配置及び圧力により発生する可能性がある組織サンプリングの較差と表面反射との影響を受けやすくなる場合がある。

【００２８】

結論

ここで実施された温度の研究は、ｉｎ－ｖｉｖｏスペクトル測定に存在する温度関連較差の収集及び特定に関して、ＦＯＣＳＩ被験者インタフェースモジュールがＤＲＡＣＯ被験

者インタフェースモジュールよりも効果的であったことを確認するために使用できる。平常時と加熱時との組織のスペクトルの差異は、吸収度単位の数百分の一程度であり、ＤＲＡＣＯ検出器のノイズの欠点は、こうした比較において重要ではない。ユニット間に残存する最も大きな差異は、光学サンプリングシステムに存在しており、ＤＲＡＣＯでは従来のレンズシステムであり、ＦＯＣＳＩでは、モノクロメータから試料へ進み、検出器へ戻る、光ファイバ光伝送システムである。有意レベルの可変皮膚表面反射率の存在と、ＤＲＡＣＯでの測定に内在する幅の広い光学経路の分布とは、１４５０ｎｍの水の帯域における拡張及び形状の不確実性につながることが予想された。Ｊ・Ｄ・ハーディ、Ｈ・Ｔ・ハメル、Ｄ・ムルガトロイドのＪ Ａｐｐｌ．Ｐｈｙｓｉｏｌ．，９：２５７（１９５６）を参照されたい。代わりに、ＦＯＣＳＩシステムは、無視可能な表面反射率コンポーネントと、測定機器に達する光子に関する試料パスレングスの狭い分布とを有すると予想された。こうしたＤＲＡＣＯとＦＯＣＳＩとの間の光学的差異は、ＤＲＡＣＯにより測定された水の帯域の情報コンテンツを少なくしていると予想された。加えて、その他の目立たない要素により、温度関連スペクトル較差の解釈は、大幅に制限又は強化されることもある。

【００２９】

望ましいことに、ＦＯＣＳＩにより取得されたスキャン結果の温度関連スペクトル較差は、水及びヒト組織の予想されるスペクトルシフト及び散乱特性と一致した。注目すべき点として、ＤＲＡＣＯでの実験では、皮膚温度による体系的なスペクトル較差を生成することに成功しなかった。ＤＲＡＣＯで取得されたスキャン結果の測定不整合の原因として最も可能性の高いものは、皮膚表面反射率の試料対試料較差である。残念なことに、同じ被験者の異なる測定間における表面反射率に僅かな違いがあっても、水の帯域の振幅及び形状に変化が生じる可能性がある。このことは、次に、温度関連スペクトル較差の解釈を困難または不可能にする。ｉｎ－ｖｉｖｏ試料散乱及び平均光学経路における関連する変化は、温度、圧力、生理的反応、及びサンプリング位置の変化と共に変わる可能性がある。温度の補正では、温度関連較差の大部分が、こうした変化に影響されないことが必要である。皮膚温度状態の分離は、温度以外の要素によるスペクトル較差がＦＯＣＳＩ機器よりも大きいため、ＤＲＡＣＯ機器では極めて困難となる。この実験で取得された測定値の一貫性と、結果として生じた情報コンテンツとから、温度関連スペクトル較差の補正には、ファイバベースの機器を使用するのが好ましいという結論が導かれる。

【００３０】

実験ＩＩ：皮膚温度プロフィール

概要

この研究の目的は、無制御及び受動的皮膚温度制御の両方での皮膚温度プロフィールを特徴付けることである。無制御及び受動的制御の皮膚温度は、両方とも、１日の初めで最も低く、１日の経過と共に安定する傾向を有することが分かった。受動制御及び無制御プロフィールは、互いに後を追う傾向があり、ただし、受動的に制御された皮膚温度は、急激な変化を受ける度合いが少なかった。

【００３１】

実験

８人の被験者を２つのグループに分け、各グループには男性３人及び女性１人を含めた。無制御及び受動的制御の皮膚温度プロフィールは、両方とも、３日間、午前９時～午後６時に、１時間毎に収集した。グループ１では、前腕部の測定部位をＴＨＥＲＭＡＸラップにより閉塞し、皮膚温度を受動的に制御した。グループ２では、１日目にＴＨＥＲＭＡＸラップを用いて受動的制御を行った。２日目及び３日目は、前腕全体を覆うフリースのアームスリーブを用いて制御した。両方のグループで、無制御の温度測定値は、閉塞していない状態にある被験者の他方の前腕部で収集した。皮膚温度の決定は、ＹＳＩ４０００温度センサを使用して行った。

【００３２】

結果と説明

初期温度は、被験者の服装に応じて変化することが観察され、長袖を身につけている被験者は高い初期温度を示した。８人の被験者全員が右利きであり、右腕部の温度が全般的に高いことが観察された。被験者の腕部温度は、必ずしも室温と相関しておらず、一般に、腕部温度は午前中に急激に上昇し、その後、安定して最終的に低下するか、または、当初の急激な上昇に比べて穏やかな形で上昇を続けた。受動的制御における毎日の最高温度は、８人のうち七人の被験者で、９１～９３°Ｆの比較的狭い範囲で発生した。毎日の最低温度は、非常に変わりやすく、コーヒー及びソフトドリンクといった刺激のある飲料の摂取により影響される場合があった。受動的制御した皮膚温度は、一般に、被験者の外出時等、外的環境の温度の急激な変化に影響されにくかった。最初の午前中の急激な温度上昇後、制御プロフィール及び無制御プロフィールは、互いに後を追う傾向があり、無制御の温度と制御された温度との間での広がりは、殆ど一定のままだった。これは、無制御の腕部と制御された腕部との間で温度を安定させる傾向がある感応反応の結果である可能性がある。最後に、前腕部全体をフリースのアームスリーブで覆うことにより、皮膚温度が約２～９°Ｆ上昇する場合があることが観察された。

【００３３】

結論

皮膚温度は、多数の環境的及び生理的影響を受けやすい。様々な受動的制御戦略の使用により、±１°Ｆの範囲が維持される程度まで、皮膚温度の変動を最小化することができる。受動的制御の適用により、皮膚温度の急激な上昇を促進することができる。

【００３４】

実験ＩＩＩ：試料の再現性に対する皮膚温度の予備的影響

概要

この研究は、皮膚温度と非侵襲性スペクトルとの関係、特に、大きな皮膚温度の偏位がサンプリング精度にどのような影響を与えるかに注目している。この研究は、３人の被験者それぞれに関して、広範囲の皮膚温度と、制御された範囲の皮膚温度とにおいて、非侵襲性スペクトルを収集する形で実施された。予備的な結果は、最低限の皮膚温度較差が１５００～１６００ｎｍ波長領域におけるスペクトル較差の低減につながることを示している。

【００３５】

序論

数回の訪問に渡って経口耐糖能テストを繰り返し受けた糖尿病被験者の第１のプールでの皮膚温度データから、任意の被験者が、訪問間及び４時間に渡る単一の訪問期間において、大きな皮膚温度較差を示す可能性があることが明らかとなっている。こうした較差は、環境的条件及び生理的条件を含め、いくつかの要素の結果である可能性がある。試料の安定性に対する大きな温度較差の影響を理解する必要がある。健康な個人の第２のプールにおける皮膚温度のモニタリングでは、通常の平日に温度が５°Ｆ程度変化することが明らかとなった。３人の参加者それぞれに関する２種類のデータセットを生成するために研究を実施した。第１のデータセットは、試料間で約８°Ｆまでの大きな皮膚温度偏位のある非侵襲性試料を含み、第２のデータセットは、２°Ｆの範囲内で制御した試料で構成される。

【００３６】

実験手順

男性２人及び女性１人の３人の被験者が、第２の研究に参加した。測定前に、測定部位は、ＲＴＶ（常温加硫）シリコンゴムのプラグにより、４５分間閉塞した。アリゾナ州テンペのＩｎｓｔｕｍｅｎｔａｔｉｏｎ Ｍｅｔｒｉｃｓ，Ｉｎｃ．が製造したＦＯＣＳＩ９（光ファイバ結合スキャニング機器）スペクトロメータ機器を利用して、データを収集した。ミネソタ州セントポールの３Ｍ Ｃｏｒｐｏｒａｔｉｏｎが供給する光結合流体、ＦＬＵＯＲＩＮＥＲＴ ＦＣ－４０を利用し、測定部位とスペクトロメータの光ファイバプローブとの間の結合を強化した。各試料で、基準スキャン（８０％反射率標準）及びポリスチレンスキャンを収集した。オハイオ州イエロースプリングのＹＳＩ，Ｉｎｃ．が供給

するＹＳＩ温度プローブを使用して、スペクトル測定部近くの皮膚温度測定値を記録した。

【００３７】

大きな皮膚温度較差及び最小化した皮膚温度較差の両方について、５～８試料を収集した。最小化した皮膚温度較差は、ここでは制御サンプルと呼び、測定腕部を小型の毛布で約９１°Ｆまで受動的に暖めることにより達成した。無制御試料は、大きな温度較差を有し、約８６°～９３°Ｆで皮膚温度が変化する試料で構成した。

【００３８】

データ分析

ベースライン修正、ｘ軸線標準化、アウトライア検出、及び吸収度への変換を含む前処理ステップを、分析前にデータセットに適用した。各試料は、１６回のラスタスキャンで構成し、アンサンブル平均化した。第１の誘導スペクトルは、３５ポイント１次Ｓａｖｉｔｓｋｙ－Ｇｏｌａｙフィルタを使用して取得した。試料の各セットの標準偏差の２乗を計算し、これをスペクトル較差とする。スペクトル較差が小さければ、ＰＬＳ（部分最小２乗）モデリングに関して、モデル化が単純になる。

【００３９】

加えて、制御及び無制御試料に関するサンプリング再現性を評価するために、ＲＭＳＥ（２乗平均平方根誤差）値を計算した。各検出器の全体的な使用可能波長領域（１．９μｍ及び２．６μｍ検出器について、それぞれ１１００～１７００ｎｍ及び１４００～２４００ｎｍ）を使用して、これらの値を決定した。

【００４０】

結果

図８は、スペクトル較差と、第１の被験者プールからの例示的な被験者に関する臨床データの波長との対比を示している。このデータは、２度の別個の通院からの試料を含む。試料は、皮膚温度に従って分離した。皮膚温度の標準偏差は、０．３８°Ｆ（８０）及び２．７３°Ｆ（８１）だった。皮膚温度較差が小さい時、１５００～１６００ｎｍスペクトル領域におけるスペクトル較差は、顕著に減少することが観察された。

【００４１】

第２の被験者プールに関する研究も、皮膚温度較差の最小化がスペクトル較差の減少につながることを示している。図９～１１は、１．９μｍ検出器のスペクトル較差と、被験者１～３の波長の対比を示している。図９ａ～１１ａは、それぞれ２．７３°Ｆ（９０、１００、１１０）及び３８°Ｆ（９１、１０１、１１１）に等しい皮膚温度の標準偏差に関するスペクトル較差のプロットを、図９ｂ～１１ｂの対応する制御及び無制御温度プロフィールと共に提示している。結果は、２．６μｍ検出器の１５００～１６００ｎｍ領域と同様である。ＲＭＳＥ値は、図１２及び１３に提示しており、データの試料再現性の間を示している。試料間格差は、温度較差が制御される時、被験者１及び２に関して、１．９μｍ検出器で緩やかに減少し、被験者２及び３に関して、２．６μｍ検出器で大きく減少した。

【００４２】

上に提示した両研究は、皮膚温度の較差が小さい試料では、対象の波長領域でのスペクトル較差が減少することを示している。

【００４３】

単一の個人での経時的な皮膚温度の変化に加えて、皮膚温度範囲は、個人間でも変化する。例えば、周囲温度と、１日の時間と、機器の被験者インタフェースモジュールとの接触に対する生理的反応と、衣服のタイプと、活動レベルとは、すべて人間の皮膚温度に影響する。多数のパラメータが関与するため、非侵襲性スペクトルを収集すべき単一の皮膚温度を定義することは不可能である。しかしながら、被験者の皮膚温度較差を最小化する方法により、対象の波長領域内でのスペクトル較差が減少することは明らかである。スペクトル較差を最小化するために、皮膚温度を約８９～９１°Ｆに維持することができる。毛布その他の熱ラッピングにより前腕部を包むことは、スキャニング前に皮膚温度を上昇さ

せる効果的な方法であり、これにより、スキャニング中に温度の大きな過渡状態が持ち込まれることはない。皮膚温度を制御する別の可能な方法には、スキャニング前に腕部を温度制御ヒートシンクに置くことが含まれる。

【００４４】

本発明について、皮膚温度の制御に関して説明したが、本発明は、水和又は表面のｐＨといった他の組織状態パラメータに応用することもできる。加えて、本発明は、非侵襲性血糖判定において独自の応用が可能であるが、本発明は、例えば、コレステロール、その他の脂質、ＢＵＮ、及びタンパク質等、血液及び組織のその他の成分の測定に応用することもできる。更に、本発明は、エタノール及びその他の様々な薬物及び毒素といった血中の異物の検出に適合することになる。

【００４５】

以上、本明細書では、特定の好適な実施形態に基づき本発明を説明してきたが、本発明の精神及び範囲から逸脱することなく他の適用例を代替し得ることは当業者には容易に理解されよう。したがって、本発明は、当該特許請求の範囲によってのみ限定されるものである。

【図面の簡単な説明】

【図１】２種類の温度で測定された水吸収ピークを示す、吸収スペクトルの図である。

【図２】本発明による、光ファイバ被験者インタフェースを有するスペクトロメータ機器で測定した２被験者の水吸収ピークを示す、吸収スペクトルの図である。

【図３】本発明による、光ファイバ被験者インタフェースを有するスペクトロメータ機器で測定した２被験者の水吸収ピークを示す、吸収スペクトルの図である。

【図４】本発明による、レンズから構築された被験者インタフェースを有するスペクトロメータ機器で測定した図２及び３の被験者の吸収スペクトルの図である。

【図５】本発明による、レンズから構築された被験者インタフェースを有するスペクトロメータ機器で測定した図２及び３の被験者の吸収スペクトルの図である。

【図６】本発明による、図２及び３の吸収スペクトルに関する差スペクトルを示す図である。

【図７】本発明による、図４及び５の吸収スペクトルに関する差スペクトルを示す図である。

【図８】本発明による、糖尿病被験者に関する波長に対するスペクトル較差のプロットを示す図である。

【図９Ａ】本発明による、健康な被験者１に関する波長に対するスペクトル較差のプロットを示す図である。

【図１０Ａ】本発明による、健康な被験者２に関する波長に対するスペクトル較差のプロットを示す図である。

【図１１Ａ】本発明による、健康な被験者３に関する波長に対するスペクトル較差のプロットを示す図である。

【図９Ｂ】本発明による、図９Ａの被験者１に関する最小化された温度較差及び大きな温度較差のプロットを示す図である。

【図１０Ｂ】本発明による、図１０Ａの被験者２に関する最小化された温度較差及び大きな温度較差のプロットを示す図である。

【図１１Ｂ】本発明による、図１１Ａの被験者３に関する最小化された温度較差及び大きな温度較差のプロットを示す図である。

【図１２】本発明による、図９～１１の３被験者に関する２種類のＬＥＤ検出器に関連した試料較差間の棒グラフを示す図である。

【図１３】本発明による、図９～１１の３被験者に関する２種類のＬＥＤ検出器に関連した試料較差間の棒グラフを示す図である。

【図１４】本発明による、組織測定部位における皮膚温度を測定及び制御する方法のブロック図である。

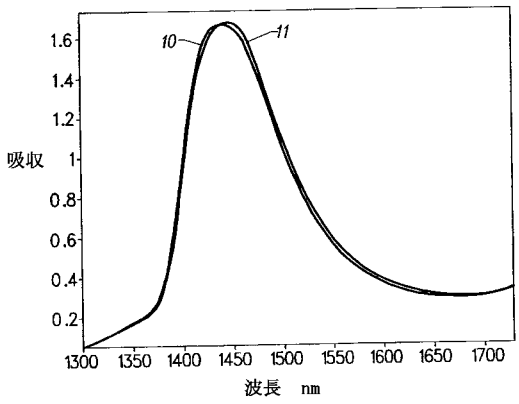
【図１５】本発明による、組織測定部位における皮膚温度を測定及び制御するスペクトロ

メータ機器のブロック図である。

【符号の説明】

１５１　被験者
１５２　被験者インタフェースモジュール
１５３　検出光学装置
１５４　光検出器
１５５　アナログ・デジタル変換機（ＡＤＣ）
１６０　光源

【図１】



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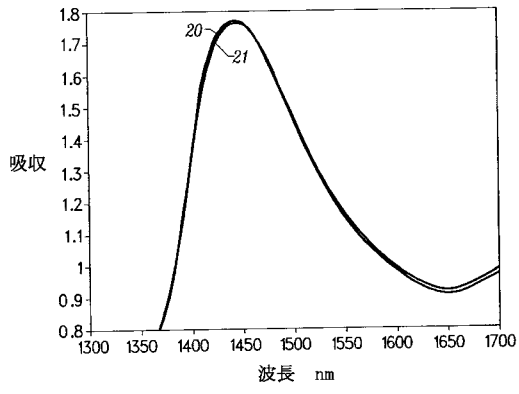

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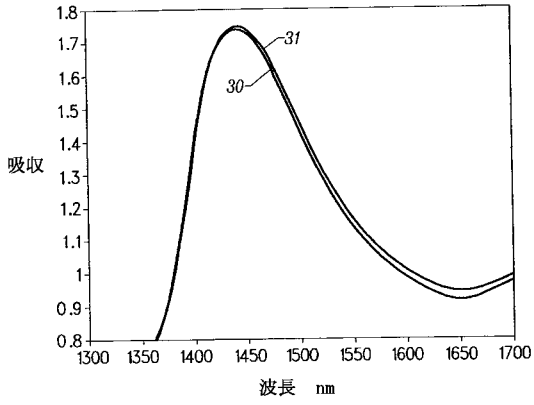

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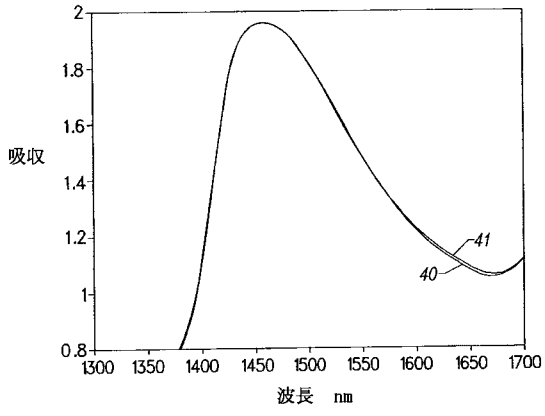

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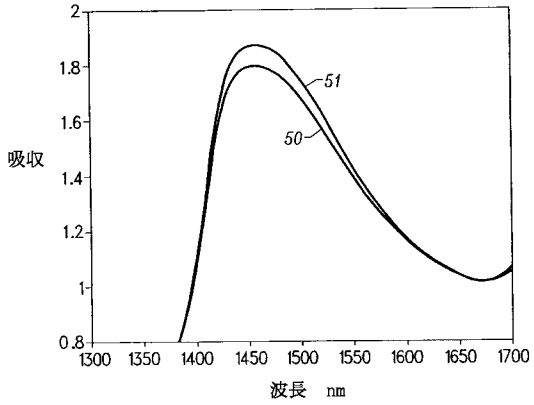

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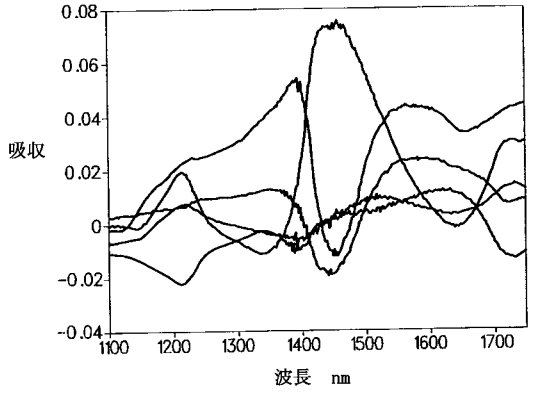

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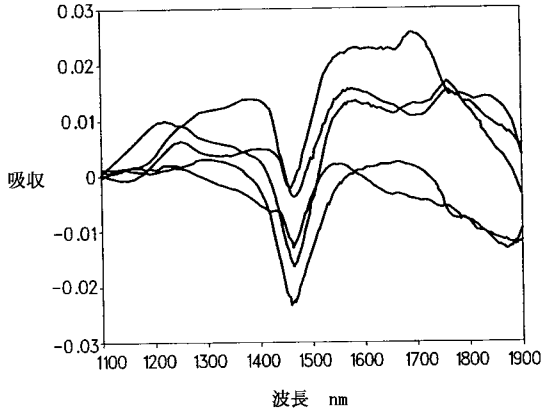

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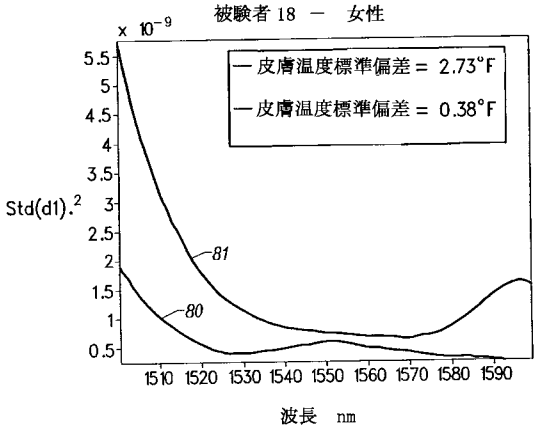

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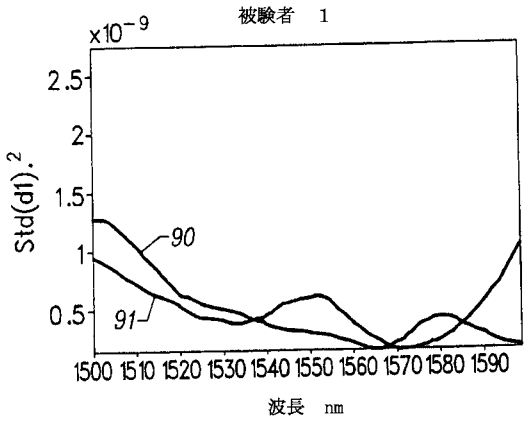

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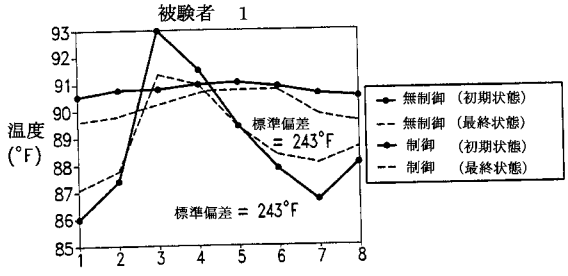

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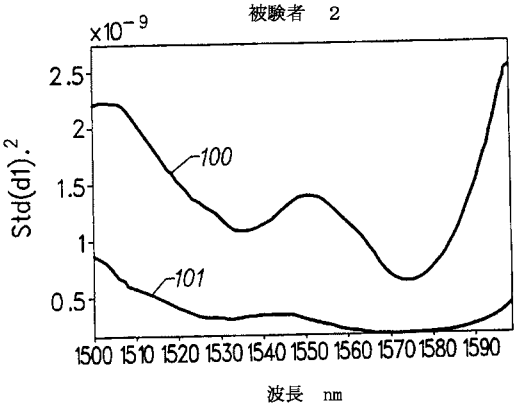

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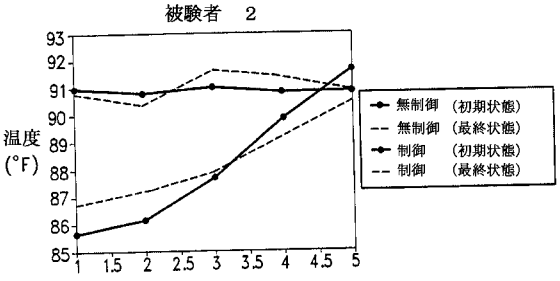

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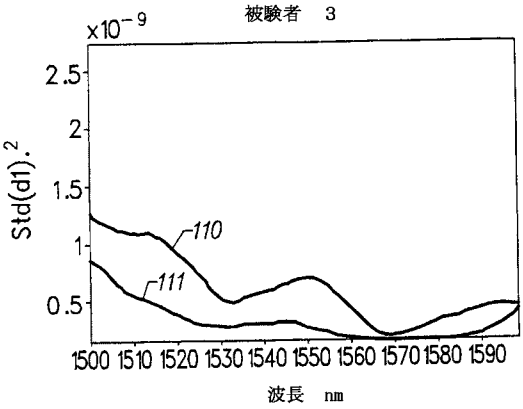

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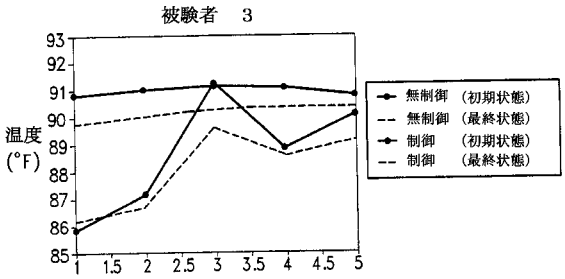

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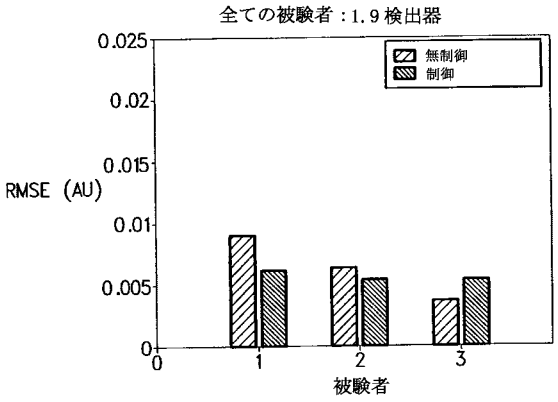

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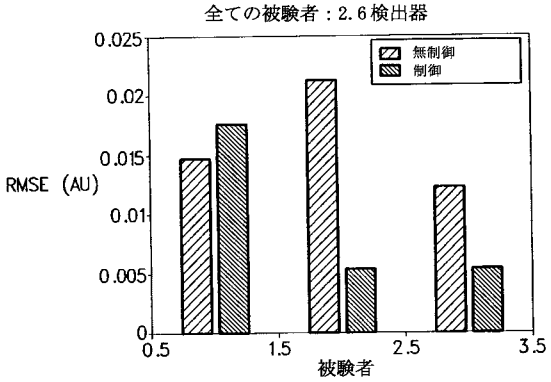

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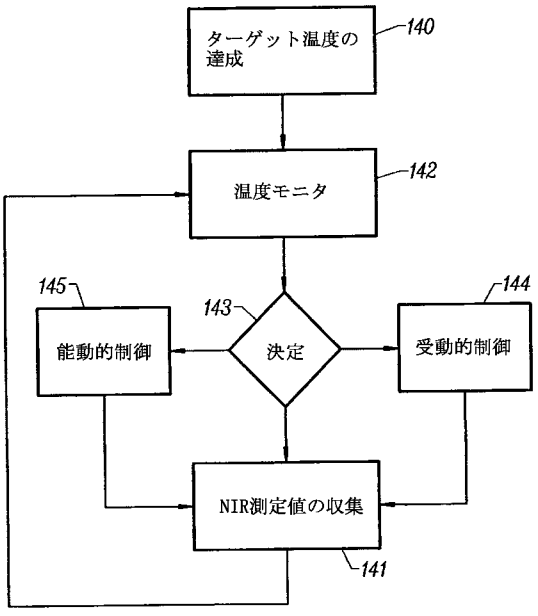

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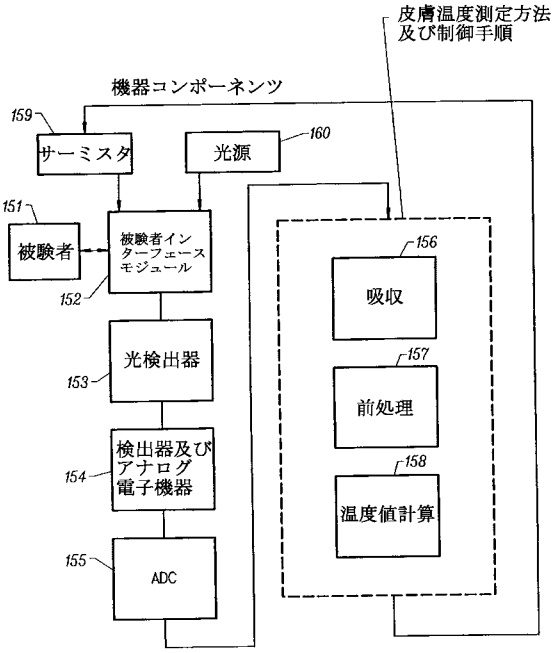

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(54) Title: MINIMIZING SPECTRAL EFFECTS DURING NIR-BASED BLOOD ANALYTE DETERMINATION

(57) Abstract: A method and apparatus for minimizing confounding effects in a noninvasive *in-vivo* spectral measurement caused by fluctuations in tissue state monitors a selected tissue state parameter within a target range, at which spectral effects attributable to the changes in the selected parameter are minimized. The invention includes means for both active and passive control in maintaining the selected tissue state parameter within the target range.

MINIMIZING SPECTRAL EFFECTS DURING NIR-BASED BLOOD ANALYTE DETERMINATION

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The invention relates to the field of noninvasive tissue constituent analysis. More particularly, the invention relates to a method and apparatus for minimizing spectral effects in NIR spectral measurements for noninvasive blood analyte determination attributable to tissue state variations.

DESCRIPTION OF RELATED ART

Near infrared (NIR) tissue spectroscopy is a promising noninvasive technology that bases measurements on the irradiation of a tissue site with NIR energy in the 700-2500 nanometer wavelength range. The energy is focused onto an area of the skin and propagates according to the scattering and absorption properties of the skin tissue. Therefore, the reflected or transmitted energy that escapes and is detected provides information about the tissue volume that is encountered. Specifically, the attenuation of the light energy at each wavelength is a function of the structural properties and chemical composition of the tissue. Tissue layers, each containing a unique heterogeneous particulate distribution, affect light absorbance through scattering. Chemical components such as water, protein, fat and blood analytes absorb light proportionally to their concentration through unique

absorption profiles or signatures. The measurement of tissue properties, characteristics or composition is based on detecting the magnitude of light attenuation resulting from its respective scattering and/or absorption properties.

While noninvasive prediction of blood analytes, such as blood glucose concentration, has been pursued through NIR spectroscopy, fluctuations in tissue state, such as skin temperature, lead to increased spectral variance that can lead to a reduction of the net analyte signal, thus rendering it difficult to extract valuable analyte information.

Human tissue can consist of as much as 80% water, which has a known peak shift that is a function of temperature, in the NIR absorbance spectrum. As temperature increases, the water band shifts to shorter wavelengths as a result of a decrease in hydrogen bonding. As light irradiates the tissue and travels through the layers of the skin, it is scattered and absorbed by the constituents of the skin before exiting the skin, where it is detected by a spectrometer. Skin temperature variation is introduced into the spectral measurement in two ways. First, the resulting signal contains spectral information from the tissue volume it has traversed, including contributions from the natural temperature gradients present in the optical sampling path of human tissue. Second, human skin and sub dermal tissue undergo temperature variations, as a result of environmental and physiological factors, to maintain a uniform core body temperature. During the course of a day, skin temperatures have been observed to fluctuate by as much as 5° F in healthy individuals. These factors result in temperature variations between the

measurements comprising a data set. Therefore, water band shifts within a measurement and between measurements are present in the data set. The data set is used to estimate the analyte of interest through the development of a multivariate mathematical calibration model.

Within and between measurement temperature variations add a level of complexity to the multivariate analysis, making it more difficult to extract valuable analyte information. Large variations in temperature lead to increased spectral variance that can lead to a reduction of the net analyte signal. In addition, uncontrolled skin temperature variations have a higher probability of correlating with analytes of interest. Such chance correlations can lead to false calibrations, which may or may not be discernible.

Various spectroscopic methods and apparatuses that aim to monitor or alter sample temperature in some way are described in the prior art. For example, J. Braig, D. Goldberger, B. Sterling, *Self-emission noninvasive infrared spectrophotometer with body temperature compensation*, U.S. Patent No. 5,615,672 (April 1, 1997) describe a "self-emission" glucose monitor that noninvasively measures glucose concentration in a subject's blood by monitoring the infrared emission of glucose in the blood at long infrared wavelengths near 10 microns. The described device utilizes the infrared energy emitted by the person's blood and/or surrounding tissue to perform the absorption analysis. A temperature-sensing device for measuring the person's internal temperature at the arm is also used to adjust the constituent concentration measurement for temperature dependent effects. While the use of the person's own infrared energy, emitted as body heat, for an infrared

source eliminates the necessity of providing an energy source, the described device and the attendant method require a determination of the individual's internal temperature; however, the sensor measures temperature at the skin surface. Therefore, the calculated compensation for internal body temperature to be applied to the measured spectral signal introduces a significant source of error in the analyte concentration estimate. Additionally, the sensor's thermal time constant introduces an undesirable latency into the measurement, possibly as long as 1 1/2 minutes. Furthermore, the described device merely calculates a correction to be made to the spectral signal that compensates for the effect of the subject's body temperature. No provision is made for control of temperature within a target range in order to provide an optimal sample temperature, at which temperature-related spectral effects are minimized. Additionally, the Braig, *et al.* teachings are concerned with the mid- and far regions of the IR spectrum.

M. Block, *Non-invasive IR transmission measurement of analyte in the tympanic membrane*, U.S. Patent No. 6,002,953 (December 14, 1999) describes non-invasive methods and apparatuses for measurement of concentrations of selected blood constituent in which an optical device is inserted into the external ear canal to direct a portion of the electromagnetic radiation onto an IR detection and analysis device. The tympanic membrane is cooled to create a temperature differential with the inner ear, thus facilitating the emission of thermal radiation across the tympanic membrane. The insertion of an optical instrument deep into the ear canal and chilling of the tympanic membrane are by no means invasive, although they may be seen to be minimally invasive compared to more traumatic methods of

sampling, such as venipuncture. The Block teachings make no provision for spectroscopy-based measurement of temperature at the measurement site. The cooling of the tympanic membrane is not done to minimize spectral effects of tissue state fluctuation, but to facilitate thermal transfer. With the exception of cooling the tympanic membrane in a stereotypical fashion, the Block device is incapable of controlling temperature at the measurement site. The Block device further provides no closed loop in which spectroscopic temperature determinations provide the feedback required for control of site temperature.

J. Braig, C.Kramer, B. Sterling, D. Goldberger, P. Zheng, A. Shulenberger, R. Trebino, R. King, C. Barnes, *Method for determining analyte concentration using periodic temperature modulation and phase detection,* U.S. Patent No. 6,161,028 (December 12, 2000) describe a method of determining the analyte concentration of a test sample that employs a rationale similar to that of Block. A temperature gradient is introduced in the test sample and infrared radiation detectors measure radiation at selected analyte absorbance peak and reference wavelengths. The Braig, *et al.* teachings employ gradient spectroscopy, in which a temperature gradient is produced in the sample to facilitate thermal transfer, thereby delivering more thermal radiation to the radiation detectors. The method described does not address the problem of spectral effects related to fluctuations in tissue state at the measurement site and their confounding effect on the net analyte signal. With the exception of inducing a temperature gradient in the sample, the described method provides no way of controlling sample temperature within a target range that minimizes the spectral effects caused by fluctuations in sample temperature.

In view of the problems left unsolved by the prior art, there exists a need for a way to control spectral effects attributable to tissue state variations, such as skin temperature, during NIR-based, non-invasive blood analyte determination, by monitoring the selected tissue state parameter and maintaining it within a predetermined target range of values at which such spectral effects are minimized. It would be a significant technological advance to monitor the tissue state parameter spectroscopically, in which a calibration model calculates measured values by correlating shifts in the selected tissue state parameter with shifts in observed spectral effects, thus eliminating the time constants imposed by conventional sensor devices. It would be desirable to provide a means of controlling the selected tissue state parameter, driven by a closed loop, in which the calculated values provided the feedback for determining the degree of control to be applied.

SUMMARY OF THE INVENTION

The invention provides a method and apparatus for minimizing confounding effects in a noninvasive *in-vivo* spectral measurement caused by fluctuations in tissue state. A selected tissue state parameter is spectroscopically monitored through the application of a multivariate calibration model that correlates spectroscopic changes with fluctuations in the selected tissue state parameter, providing near-instantaneous measurements, without the imposition of any significant time constants. A target range of values for the selected parameter is empirically determined from an experimental data set

by observing the spectra of the data set to determine a range of values at which spectral effects due attributable to the changes in the selected parameter are minimized. During measurement, the selected parameter is continuously monitored. The calculated values provide feedback in a closed loop that drives a device for maintaining the selected tissue state parameter within the target range. Means for both active and passive control of the tissue state parameter are included in the invention.

A preferred embodiment of the invention provides a method and apparatus for minimizing the confounding effects in a noninvasive near IR spectral measurement attributable to shifts in skin temperature at the tissue measurement site. Skin temperature at the measurement site is spectroscopically monitored by calculating temperature values through the application of a multivariate calibration model that correlates spectroscopic changes with shifts in skin temperature. Thermal time constants imposed by conventional temperature sensing devices are eliminated, providing near-instantaneous temperature readings. Active and passive control means are provided. Passive control is achieved through the selective application and removal of an occlusive thermal wrap. Active control is provided by a thermistor applied to the skin in the vicinity of the measurement site. Active and passive control may be applied in complementary fashion or they may be used separately. In a particularly preferred embodiment of the invention, the control means is incorporated into the measurement instrument, wherein the calculated skin temperature values provide the feedback in a closed loop that drives the control device. In an alternate embodiment of the invention, the temperature values are supplied to an operator, who then applies active

and/or passive control to achieve and maintain a skin temperature within the target range. By monitoring skin temperature spectroscopically and employing methods of passive and/or active control it is possible to reduce the effects of skin temperature variation on the NIR measurement. The invention finds particular application in the noninvasive measurement of blood glucose concentration.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides absorbance spectra, showing a water absorbance peak, measured at two different temperatures;

Figures 2 and 3 provide absorbance spectra, showing a water absorbance peak, of two different subjects measured on a spectrometer instrument having a fiber optic subject interface, according to the invention;

Figures 4 and 5 provide absorbance spectra of the subjects of Figures 2 and 3, measured on a spectrometer instrument having a subject interface constructed from lenses, according to the invention;

Figure 6 shows difference spectra for the absorbance spectra of Figures 2 and 3, according to the invention;

Figure 7 shows difference spectra for the absorbance spectra of Figures 4 and 5, according to the invention;

Figure 8 presents a plot of spectral variance versus wavelength for a diabetic test subject, according to the invention;

Figures 9a through 11a provide plots of spectral variance versus wavelength for three healthy subjects, according to the invention;

Figures 9b through 11b provide plots of minimized and large temperature variation for the three subjects of Figures 9a – 11a, according to the invention;

Figures 12 and 13 provide bar graphs of between sample variation relative to two different LED detectors for the three subjects of Figures 9 –11, according to the invention;

Figure 14 provides a block diagram of a method for measuring and controlling skin temperature at a tissue measurement site, according to the invention; and

Figure 15 provides a block diagram of a spectrometer instrument for measuring and controlling skin temperature at a tissue measurement site, according to the invention.

DETAILED DESCRIPTION

Skin Temperature Measurement and Control Using NIR Spectroscopy

Near Infrared measurements of skin combined with associated skin temperature reference measurements are used to develop NIR temperature calibrations that require only NIR tissue scans to predict skin surface temperature. Methods of developing calibrations for spectral analysis may employ a variety of multivariate analytical techniques that are well known to those skilled in the art. NIR skin temperature calibration is made possible by the known shifting of the 1450 nm water band with variations in skin temperature. The calibration model incorporates the shift information implicitly in the multivariate regression coefficients. Temperature measurement and control of human tissue is important in noninvasive NIR measurement because it provides a means of simplifying the complex overlapping spectral effects that inhibit extraction of the analyte signal. The extra temperature measurement hardware and the associated cost and complexity are avoided by using NIR temperature measurement.

An advantage of the NIR measurement over the primary thermistor measurement lies in the absence of thermal time constant inherent in conventional sensing hardware. Measured skin thermistor response frequently requires as much as 1 1/2 minutes to reflect 95% of the sample temperature change under a step change of 10° F. Eliminating the time constant in the temperature measurement provides significant advantages in the implementation of active closed-loop temperature control of the skin by providing near-immediate skin temperature feedback unimpeded by the time constant inherent in primary measurement methods.

Skin temperature calibrations for multiple individuals have been established using the calibration data from a single subject. This result foretells the feasibility of general skin temperature calibrations that can be established on site prior to the shipment of the instrument.

Procedures for active and passive control of skin temperature are provided below. Near infrared (NIR) tissue spectroscopy is utilized to irradiate the skin and estimate biological analytes of human subjects. Skin temperature variation is destructive to the NIR measurement in two ways: First, false calibrations can occur if skin temperature correlates to analytes of interest, and second, large skin temperature fluctuations decrease the net analyte signal. An apparatus and procedure to passively and actively control skin temperature to prevent decreasing the net analyte signal and spurious correlations is described. The procedure for controlling skin temperature involves determining the target skin temperature, monitoring the actual skin temperature, and applying passive and/or active control methods to attain the target temperature.

Experiments were conducted to:

- Characterize the effects of skin temperature variation on the NIR spectrum – see Experiments I and II, below.
- Characterize skin temperature profiles over the course of a day and between days, and to determine target temperatures – see Experiment II and III, below.
- Test methods of controlling skin temperature to within ± 1° F – see Experiment III, below.

Methods of Skin Temperature Control

One of the primary functions of the skin is to maintain a constant body temperature. Physiological responses to external and internal stimuli can limit skin temperature control. Periodic monitoring is a critical step in achieving good temperature control. Using the invention, the skilled practitioner is enabled to discern trends in skin temperature and implement passive and/or active control as compensation, thus maintaining a stabilized skin temperature at the spectral measurement site.

Skin temperature is monitored using a temperature probe attached to the skin within 5 mm of the spectral measurement site. As the discussion of Experiment II, below shows, daily skin temperature profiles have shown that temperatures are generally lower in the morning and gradually increase throughout the day, resulting in a profile with a gentle positive slope that stabilizes with time. As indicated in the discussion of Experiment III, below, healthy and diabetic skin temperature profiles have resulted in an initial target skin temperature range of 90-92° F, representative of temperatures observed in the mid- to late afternoon. Target ranges may vary depending on the individual. The following methods are utilized to achieve and maintain the target range:

PASSIVE CONTROL

Passive control, by means of a thermal wrap placed around the subject's forearm, can be implemented to quickly drive the skin temperature to the target temperature in the morning. This results in a profile with a steep positive slope during the first hour, followed by more uniform skin temperatures during the rest of the day. The wrap covers the forearm from the wrist to elbow and, therefore raises the temperature of the entire forearm. The wrap can be adjusted loosely or snuggly around the subjects arm, or removed, as needed to maintain the skin temperature within the target range.

ACTIVE CONTROL

Active control utilizes a temperature-controlled copper heat sink to rapidly change the temperature of the skin. The set point of the heat sink can be adjusted to warm or cool the skin. Active control is localized to the skin that comes into contact with the heat sink, which has the same dimensions as the subject-spectrometer interface. If the skin temperature is significantly outside of the target range just prior to the spectral measurement, the arm is placed on the heat sink for 1-2 minutes before the measurement.

The methods presented above can be used in a complementary fashion to maintain skin temperature within the target range. The method chosen is a function of the time available before the spectral measurement and observed skin temperature. The decision to implement active or passive control is made each time the skin temperature is monitored based upon the time available before the spectral measurement and the difference between the actual and target temperatures. Passive control is best suited for time periods greater

than 1-2 minutes, whereas active control is advantageous if rapid temperature increases or decreases are required. A flow diagram of a general procedure to control skin temperature is presented in Figure 14. As described herein, a target temperature is established 140 empirically by observing spectral measurements and establishing a target range at which spectral variation is kept to a minimum. NIR spectral measurements are collected 141, and skin temperature is monitored 142 spectroscopically by the application of a multivariate calibration to the spectral measurement that correlates spectral effects with skin temperature. The temperature reading is evaluated 143. If skin temperature is within the target range, no control is implemented. If the skin temperature is outside of the target range, either passive 144 or active 145 control, or a combination of both, are implemented to bring temperature back into the target range. It can be seen from Figure 14 and 15 that the system of the current invention represents a closed loop, in which the control devices are driven by the feedback supplied by the spectroscopic temperature determinations.

A spectrometer instrument for implementing the invented method is shown in Figure 15. A subject interface module 152 is coupled with a tissue measurement site on the skin of the subject 151. A thermistor 159 mounted within the subject interface module has a set point within the target range. In order to maintain its set point, the thermistor either heats or cools the skin surface. In a preferred embodiment of the invention, the subject interface module comprises a fiber optic probe. The subject interface module directs light emitted from the light source 160 toward the tissue measurement site. Light that is back diffused form the tissue measurement site is directed toward

one or more photo detectors 154 by detector optics 153, in this case, a fiber optic. Analog electronics convert the detected light to a voltage, which is subsequently converted to a digital value by an analog-to-digital converter (ADC) 155. From these digital values, an absorbance spectrum is calculated 156. The absorbance spectrum may be subjected to one or more of the pre-processing techniques 157 previously described. Subsequently, a temperature value is calculated 158 from the absorbance spectrum through the application of the calibration model previously described. Finally, the calculated temperature value is routed to a controller (not shown) that interfaces with the thermistor 159, to provide temperature feedback.

EXPERIMENT I: Impact of Skin Temperature on NIR Spectra

SUMMARY

A preliminary study was conducted in order to determine if the optical configuration of the FOCSI (fiber optic coupled scanning instrument) spectrometer instrument, supplied by Instrumentation Metrics, Inc., Tempe AZ, was superior to the optical configuration of the DRACO spectrometer instrument, also supplied by Instrumentation Metrics, Inc. with respect to the information content contained in the water band of the NIR spectrum. The water band at 1450 nm is known to shift with sample temperature, rendering the modeling of glucose in water and tissue more difficult over samples that are taken at widely varying temperatures. Therefore, a blood glucose prediction algorithm must incorporate a calibration strategy that utilizes the shift in the water band to simplify the modeling challenges. Thus, an optical

design that permits evaluation of tissue temperature information is an important design criterion for a noninvasive glucose monitor. In this study, it was observed that noninvasive measurements taken at different temperatures on the FOCSI instrument were substantially more consistent with the expected spectral behavior than those taken on the DRACO. It is suspected that the highly variable sample pathlength inherent in the noninvasive DRACO measurement confounds the interpretation of temperature effects.

INTRODUCTION

Water, comprising as much as 80% of human tissue, has a known peak shift in the NIR absorbance spectrum with increasing sample temperature. The shift of the water band to shorter wavelength arises as a result of the increased solution pH and a concomitant decrease in hydrogen bonding with increasing temperature. In Figure 1, the transmission spectrum of the first-overtone band of water is plotted at 33 (11) and 41 (10) degrees centigrade. An *in vivo* measurement peak can be expected to contain spectral contributions from a distribution of temperature states due to a natural temperature gradient present in the optical sampling path of human tissue. Modeling glucose in this thermally complex sample matrix is one of the more significant challenges of *in vivo* measurement using NIR spectroscopy. Accurate compensation for tissue temperature is best approached by inference from the spectral measurement because probing tissue with near infrared light is likely to lead to localized effects on the surface and in the tissue. A temperature probe cannot be inserted into the light path of the spectrometer without disturbing the measurement and a non-invasive temperature probe will not account for temperature gradients in tissue. The

most effective means of compensating for tissue temperature variation requires that the measured spectrum contain substantive information about the position and shape of the water band. The shape of the water band is also influenced by tissue optics, making the acquisition of highly informative spectral scans even more important. In light of these considerations, instrumental or sampling artifacts that distort the shape of the water band are highly undesirable and should strongly influence the design of non-invasive glucose instrumentation based on NIR spectroscopy.

EXPERIMENTAL

Six subjects were scanned on both the FOCSI and DRACO scanning spectrometers. Two sets of experiments were conducted on each subject. In the first experiment, the subject was scanned at normal ambient skin temperature, while the second experiment was conducted after preheating subjects' skin temperature to 3-5° F above the normal skin temperature. Measurements taken prior to the study led to the establishment of the following protocols for spectrum measurement: Rapid temperature and physiological changes were reduced by allowing 3 minutes of arm contact with the instrument subject interface module prior to the acquisition of spectra. A YSI 4000 skin temperature sensor, supplied by YSI, Inc., Yellow Springs OH, with a readout to ±0.05° F was placed about 5mm from the measurement site during the course of the experiments. Temperature was recorded every 30 seconds and scans were conducted over a period of two minutes. Reference spectra using an 80% reflectance standard were acquired directly before and after the *in vivo* measurement.

RESULTS AND DISCUSSION

Scans taken on each spectrometer instrument were examined for temperature related effects for each of the six subjects. Temperature related effects that are consistent with a change in the temperature distribution of sample tissue were noted in three of the four remaining patients scanned on the FOCSI, but temperature related effects were not as obvious in the scans taken on the DRACO. In Figures 2 and 3, the scans taken on the FOCSI from two individuals at two temperature levels are plotted. One set of spectra were taken at skin temperatures 5° F (21, 30) higher than the other (21, 31). It is evident that the higher temperature scans had greater difference in intensity between the 1450 nm maximum and the minimum absorbance at 1650-1700 nm. The edge of the high temperature spectrum peak is also on the inside of the low temperature spectrum on the long wavelength side of the 1450 nm water band. These spectral differences are consistent with the existence of a more narrow range of water temperatures in the heated tissue, giving rise to a sharper peak. According to scattering theory, the scattering of tissue increases with temperature. The spectral region with the most dominant scattering effects is in the short wavelength region around the second-overtone band at 1100-1300 nm. Scattering is believed to diminish rapidly after the second overtone region. Suppression in the sample absorbance with increasing temperature is consistent with the expected optical behavior of tissue. The absorbance decrease from increased scattering with temperature is pronounced at the second overtone, but it may also be significant at the first overtone on highly absorbed spectral features like the maximum of the water band.

The corresponding scans 40, 50 and 41, 51 taken on the DRACO are plotted in Figures 4 and 5. As previously mentioned, temperature effects are not nearly as noticeable as they are in the spectra of Figures 2 and 3. Difference spectra calculated using the individual subject spectra taken at cool and warm skin temperatures should contain spectral information related to temperature changes in the tissue. A consistent measurement should yield difference spectra of similar shape for each of the individual test subjects. The spectra acquired for each subject at cool and warm skin temperature were subtracted and the resulting difference spectra for the DRACO spectrometer are plotted in Figure 6 and those for the FOCSI instrument are plotted in Figure 7. Clearly the difference spectra (Cold minus hot) are more consistent in shape for the FOCSI experiments than for the measurements taken with the DRACO. The temperature-induced scattering effects around the second-overtone region are consistent with scattering research for the FOCSI in that the cold minus the hot spectrum consistently yielded the positive residual expected from increased scattering by tissue at elevated temperature. It is obvious from Figures 6 and 7 that interpretations of measurements on tissue at normal and warmed temperature states using the DRACO optical system were not as simple as the corresponding measurements taken on the FOCSI. The DRACO optical system may be more susceptible to variations in tissue sampling and surface reflection that may arise due to sensor positioning and pressure.

Conclusions

The temperature studies conducted here can be used to confirm that the

FOCSI subject interface module was more effective than the DRACO subject interface module for collection and identification of temperature-related variation present in *in vivo* spectral measurements. Differences in the spectra of normal and heated tissue were on the order of several hundredths of an absorbance unit, making the noise disadvantage of the DRACO detectors a non-issue in these comparisons. The greatest remaining difference between the units was in the optical sampling systems: The DRACO with a conventional lens system and the FOCSI with a fiber optic light transport system running from the monochromator to the sample and back to the detectors. The presence of a significant level of variable skin surface reflectance and a wider optical path distribution inherent to the DRACO measurements was expected to lead to broadening and shape uncertainty in the water band at 1450 nm. See J.D. Hardy, H.T. Hammel, D. Murgatroyd, J Appl. Physiol., 9:257(1956). Alternately, the FOCSI system was expected to have a negligible surface reflectance component and a more narrow distribution of sample pathlengths for photons that reach the instrument detectors. These optical differences between the DRACO and the FOCSI were expected to contribute to lower information content in the water band measured by the DRACO. Additionally, other, less obvious factors would significantly limit or enhance the interpretation of temperature related spectral variation.

It was encouraging that temperature related spectral variation of scans taken on the FOCSI was consistent with the expected spectral shift and optical scattering properties of water and human tissue. Significantly, experiments on the DRACO were not as successful at producing systematic spectral variation

with skin temperature. The most likely source of the measurement inconsistency of scans taken on the DRACO is the sample-to-sample variation in skin surface reflectance. Unfortunately, even modest changes in surface reflectance between different measurements of the same subject can lead to changes in the amplitude and shape of the water band, which in turn make the interpretation of temperature-related spectral variation difficult or impossible. *In vivo* sample scattering and the related changes in mean optical path can vary with changes in temperature, pressure, physiological response, and sampling location. Compensation for temperature requires that temperature-related variation could be largely separated from these other effects. Resolution of skin temperature states is made substantially more challenging on the DRACO instrument because the spectral variation due to factors other than temperature is larger than for the FOCSI instrument. The consistency of the measurements taken in this experiment and the resulting information content lead to the conclusion that a fiber-based instrument is preferred for use in compensation of temperature-related spectral variation.

EXPERIMENT II: Skin Temperature Profiles

SUMMARY

The objective of the current study was to characterize skin temperature profiles, both uncontrolled and with passive skin temperature control. Both uncontrolled and passively controlled skin temperatures were found to be lowest early in the day, with a tendency to stabilize as the day progressed. The passively controlled and the uncontrolled profiles tended to track each

other, although passively controlled skin temperature were less susceptible to sudden changes.

EXPERIMENTAL

Eight subjects were divided into two groups, each group including three males and one female. Both uncontrolled and passively controlled skin temperature profiles were collected on an hourly basis between 9AM and 6PM for three days. For group one, skin temperature was passively controlled by occluding a measurement site on the forearm with a THERMAX wrap. For group two, passive control was by means of the THERMAX wrap on day one. On days two and three, control was by means of a fleece arm sleeve that covered the entire forearm. For both groups, the uncontrolled temperature measurements were collected on the subjects' other forearms, which were left unoccluded. Skin temperature determinations were made using a YSI 4000 temperature sensor.

RESULTS AND DISCUSSION

It was observed that initial temperature was dependent on subjects' clothing: subjects wearing long sleeves had higher initial temperatures. All eight subjects were right-handed, and it was observed that right arm temperatures were generally higher. Subjects' arm temperatures did not necessarily correlate with room temperature; typically arm temperature rose steeply in the morning, then it either stabilized and eventually dropped, or continued to rise in a more gradual fashion than the initial steep rise. The day-to-day highest

temperature in the passive controls occurred in a relatively narrow range of 91-93° F for seven of the eight subjects. Day-to-day lowest temperature was highly variable and may have been affected by ingestion of stimulant beverages such as coffee and soft drinks. Passively controlled skin temperatures were generally less susceptible to sudden changes in temperature of the external environment, such as when the subject went outside. After the initial AM rapid temperature increase, the controlled and the uncontrolled profiles tended to track each other, with the spread between uncontrolled and controlled temperatures remaining fairly constant. This may have been a result of a sympathetic response that tended to stabilize temperatures between the uncontrolled arm and the controlled arm. Finally, it was observed that skin temperature could by increased approximately 2-9° F by covering the entire forearm with the fleece arm sleeve.

CONCLUSIONS

Skin temperature is subject to a number of environmental and physiologic influences. The use of various passive control strategies can minimize skin temperature fluctuations to such a degree that a range of ± 1° F may be maintained. Application of passive temperature controls can precipitate rapid increases in skin temperatures.

EXPERIMENT III: Preliminary effects of skin temperature on sample repeatability

SUMMARY

The current studies focus on the relationship between skin temperatures and noninvasive spectra, in particular, how large skin temperature excursions impact sampling precision. A study was conducted in which noninvasive spectra were collected over a large range of skin temperatures as well as over a controlled range of skin temperatures for each of three subjects. Preliminary results indicate that minimal skin temperature variation leads to a reduction of the spectral variance in the 1500-1600 nm wavelength region.

INTRODUCTION

Skin temperature data from a first pool of diabetic test subjects undergoing repeated oral glucose tolerance tests over several visits show that any given subject may exhibit large skin temperature variations between visits as well as over the course of a single visit of four hours' duration. These variations may result from several factors, including environmental and physiological conditions. It is necessary to understand the impact of large temperature variations on between sample stability. Monitoring skin temperature in a second pool of healthy individuals revealed that temperatures vary as much as 5° F in the course of a typical workday. A study was conducted to generate two sets of data for each of three participants. The first data set contained noninvasive samples with large skin temperature excursions of up to approximately 8° F between samples, while the second data set consisted of samples that were controlled within a 2° F range.

EXPERIMENTAL PROCEDURE

Three subjects, 2 males and 1 female, participated in the second study. Prior to measurement, the measurement site was occluded with a plug of RTV (room temperature vulcanizing) silicone rubber for forty-five minutes. A FOCSI 9 (fiber optic coupled scanning instrument) spectrometer instrument, manufactured by Instrumentation Metrics, Inc. of Tempe AZ was employed to collect all data. An optical coupling fluid, FLUORINERT FC-40, supplied by 3M Corporation, St. Paul MN, was employed to enhance coupling between the measurement site and the fiber optic probe of the spectrometer. A reference scan (80% reflectance standard) and a polystyrene scan were collected with each sample. YSI temperature probes, supplied by YSI, Inc. of Yellow Springs OH were used to record skin temperature measurements near the spectral measurement site.

Five to eight samples were collected for both large and minimized skin temperature variation. Minimized skin temperature variation, herein referred to as controlled samples, was achieved by passively warming the measurement arm to approximately 91° F with a small blanket. Uncontrolled samples, having large temperature variations, consisted of samples with skin temperatures varying from approximately 86° to 93° F.

DATA ANALYSIS

Preprocessing steps, including baseline correction, x-axis standardization, outlier detection, and conversion to absorbance were applied to the data set prior to analysis. Each sample, consisting of 16 raster scans was ensemble

averaged. First derivative spectra were obtained using a thirty-five point first order Savitsky-Golay filter. The square of the standard deviation of each set of samples was calculated and is referred to as the spectral variance. The smaller the spectral variance, the simpler the matrix is for PLS (partial least squares) modeling.

In addition, RMSE (root mean square error) values were calculated to assess the sampling repeatability for controlled and uncontrolled samples. The entire usable wavelength regions for each detector (1100-1700 nm and 1400-2400 nm for the 1.9 μm and 2.6 μm detectors, respectively) were used to determine these values.

RESULTS

Figure 8 presents the spectral variance versus wavelength for clinic data for an exemplary subject from the first subject pool. The data includes samples from two separate clinic visits. Samples were separated according to skin temperature. The standard deviations of the skin temperatures were 0.38° F (80) and 2.73° (81) F. When the skin temperature variations are small, spectral variance in the 1500-1600 nm spectral region is observed to be noticeably reduced.

The study involving the second subject pool also indicates that minimization of skin temperature variation leads to reduced spectral variance. Figures 9 –11 through present the spectral variance for the 1.9 μm detector versus wavelength for subjects 1 through 3. Figures 9a –11a provide plots of spectral variance for standard deviation of skin temperatures equal to 2.73° F (90, 100,

110) and .38° F (91, 101, 111) respectively, along with corresponding controlled and uncontrolled temperature profiles in Figure 9b-11b. Results are similar for the 1500-1600 nm region of the 2.6-μm detector. RMSE values are given in Figures 12 and 13, which indicate between sample repeatability of the data. Between-sample variation was moderately reduced on the 1.9-μm detector for subjects 1 and 2 and greatly reduced on the 2.6-μm detector for subjects 2 and 3 when temperature variation was controlled.

Both studies presented above suggest that samples with smaller variations in skin temperature result in reduced spectral variance in the wavelength region of interest.

In addition to skin temperature varying over time in a single individual, skin temperature ranges vary between individuals. For example, ambient temperature, time of day, physiological response to contact with the subject interface module of the instrument, the type of clothing and activity level all impact a person's skin temperature. Due to the large number of parameters involved, it is not feasible to define a single skin temperature at which noninvasive spectra should be collected. However, it is clear, that a method of minimizing skin temperature variation within a subject be reduces spectral variation within the wavelength region of interest. To minimize spectral variation, skin temperatures may be maintained at approximately 89-91° F. Wrapping the forearm with a blanket or other thermal wrapping is an effective method of raising the skin temperature prior to scanning and does not introduce large temperature transients during scanning. Another possible method of controlling skin temperature involves placing the arm on a

temperature-controlled heat sink prior to scanning.

While the invention has been described herein with respect to control of skin temperature, the invention may also be applied to other tissue state parameters such as hydration or surface pH. Additionally, while the invention finds particular application in noninvasive blood glucose determination, the invention also is applicable to the measurement of other constituents of blood and tissue; for example, cholesterol, other lipids, BUN, and protein. Furthermore, the invention would be suitable for the detection of foreign substances in the blood such as ethanol and various other drugs and toxins.

Although the invention has been described herein with reference to certain preferred embodiments, one skilled in the art will readily appreciate that other applications may be substituted without departing from the spirit and scope of the present invention. Accordingly, the invention should only be limited by the Claims included below.

CLAIMS

What is claimed is:

1. A method for controlling spectral effects attributable to tissue state variations during NIR-based, non-invasive blood analyte determination, comprising the steps of:

determining a target range of values for a selected tissue state parameter;

providing means for modifying said tissue state parameter;

providing a calibration model that correlates said spectral effects to variations in said tissue state parameter;

monitoring said tissue state parameter by measuring an NIR spectrum and calculating values for said parameter from said spectrum according to said calibration model; and

if said calculated value is outside of said target range, modifying said tissue state parameter until a measured value for said parameter is within said target range.

2. The method of Claim 1, wherein said tissue state parameter comprises skin temperature in the vicinity of a tissue measurement site on a body part of a live subject.

3. The method of Claim 2, said spectral effects comprising shifts in a peak water absorbance band in an NIR spectrum, wherein said peak water absorbance band shifts to shorter wavelengths as skin temperature increases

and wherein said peak water absorbance band shifts to longer wavelengths as skin temperature decreases;

wherein said shifts attenuate a net analyte signal.

4. The method of Claim 3, wherein said peak water absorbance band occurs in a wavelength region at approximately 1450 nm.

5. The method of Claim 3, wherein said target range comprises a range of skin temperatures wherein said shifts are minimized, so that said attenuation of said net analyte signal is minimized.

6. The method of Claim 5, wherein said target range is approximately eight-nine to ninety one degrees, Fahrenheit.

7. The method of Claim 3, wherein said step of determining a target range comprises:

empirically determining said target range by examining spectra from a calibration data set to determine a temperature range in which said shifts are minimized.

8. The method of Claim 2, wherein said means for modifying a tissue state parameter comprises one or both of:

means for actively controlling said skin temperature; and

means for passively controlling said skin temperature.

9. The method of Claim 8, wherein said active means and said passive means are employed in complementary fashion to maintain skin within said target range.

10. The method of Claim 9, wherein said active means of control is employed to induce rapid changes in skin temperature.

11. The method of Claim 8, wherein said passive means of control is employed for relatively longer time periods.

12. The method of Claim 8, wherein said means for passively controlling said skin temperature comprises a thermal wrap applied to said body part, wherein initial application of said thermal wrap causes a rise in skin temperature.

13. The method of Claim 12, wherein skin temperature is maintained within said target range by one of loosening, tightening and removing said thermal wrap.

14. The method of Claim 8, wherein said means for actively controlling said skin temperature comprises a temperature-controlled heat sink.

15. The method of Claim 14, wherein said heat sink has a set point within said target range, and wherein said heat sink cools or warms said skin to maintain skin temperature within said target range.

16. The method of Claim 14, wherein active control is localized to skin that comes into contact with said heat sink.

17. The method of Claim 3, wherein said step of providing said calibration model comprises developing said calibration model using a calibration data set that includes spectral measurements on a group of exemplary subjects combined with associated skin temperature reference measurements.

18. The method of Claim 17, wherein said reference measurements span a range approximately equal to or greater than said target range.

19. The method of Claim 17, wherein said reference measurements are made using a noninvasive temperature sensor placed in the immediate vicinity of the tissue measurement site.

20. The method of Claim 17, wherein said calibration is developed using multivariate analytical techniques, and wherein said model implicitly incorporates said shift information in multivariate regression coefficients.

21. The method of Claim 20, wherein said step of monitoring said tissue state parameter comprises the steps of:

calculating an absorbance spectrum from said NIR spectrum;

optionally, pre-processing said absorbance spectrum; and

calculating a skin temperature value by applying said multivariate calibration model.

22. The method of Claim 21, wherein said step of modifying said tissue state parameter comprises applying said means of control so that skin temperature is restored to said target range.

23. An apparatus for controlling spectral effects attributable to tissue state variations during NIR-based, non-invasive blood analyte determination, comprising:

means for modifying a selected tissue state parameter;

means for measuring an NIR spectrum at a tissue measurement site;

a calibration model that correlates said spectral effects to variations in said tissue state parameter;

means for monitoring said tissue state parameter by measuring an NIR spectrum and calculating values for said parameter from said spectrum according to said calibration model;

wherein said tissue state parameter is modified by said modifying means if said calculated value is outside of a target range until said parameter is within said target range.

24. The apparatus of Claim 23, wherein said tissue state parameter comprises skin temperature in the vicinity of a tissue measurement site on a body part of a live subject.

25. The apparatus of Claim 24, said spectral effects comprising shifts in a peak water absorbance band in an NIR spectrum, wherein said peak water absorbance band shifts to shorter wavelengths as skin temperature increases

and wherein said peak water absorbance band shifts to longer wavelengths as skin temperature decreases;

wherein said shifts attenuate a net analyte signal.

26. The apparatus of Claim 25, wherein said peak water absorbance band occurs in a wavelength region at approximately 1450 nm.

27. The apparatus of Claim 25, wherein said target range comprises a range of skin temperatures wherein said shifts are minimized, so that said attenuation of said net analyte signal is minimized.

28. The apparatus of Claim 27, wherein said target range is approximately eight-nine to ninety one degrees, Fahrenheit.

29. The apparatus of Claim 25, wherein target range is empirically determined by examining spectra from a calibration data set to determine a temperature range in which said shifts are minimized.

30. The apparatus of Claim 24, wherein said means for modifying a tissue state parameter comprises one or both of:

means for actively controlling said skin temperature; and

means for passively controlling said skin temperature.

31. The apparatus of Claim 30, wherein said active means and said passive means are employed in complementary fashion to maintain skin within said target range.

32. The apparatus of Claim 31, wherein said active means of control is employed to induce rapid changes in skin temperature.

33. The apparatus of Claim 30, wherein said passive means of control is employed for relatively longer time periods.

34. The apparatus of Claim 30, wherein said means for passively controlling said skin temperature comprises a thermal wrap applied to said body part, wherein initial application of said thermal wrap causes a rise in skin temperature.

35. The apparatus of Claim 34, wherein skin temperature is maintained within said target range by one of loosening, tightening and removing said thermal wrap.

36. The apparatus of Claim 30, wherein said means for measuring an NIR spectrum comprises a NIR spectrometer instrument, wherein said spectrometer instrument includes a subject interface module

37. The apparatus of Claim 36, wherein said means for actively controlling said skin temperature comprises a temperature-controlled heat sink.

38. The apparatus of Claim 36, wherein said heat sink is incorporated into said subject interface module, so that said heat sink is in contact with said tissue measurement site during use.

39. The apparatus of Claim 37, wherein said heat sink has a set point within said target range, and wherein said heat sink cools or warms said skin to maintain skin temperature within said target range.

40. The apparatus of Claim 37, wherein active control is localized to skin that comes into contact with said heat sink.

41. The apparatus of Claim 25, wherein said calibration model is developed using a calibration data set that includes spectral measurements on a group of exemplary subjects combined with associated skin temperature reference measurements.

42. The apparatus of Claim 41, wherein said reference measurements span a range approximately equal to or greater than said target range.

43. The apparatus of Claim 41, wherein said reference measurements are made using a noninvasive temperature sensor placed in the immediate vicinity of the tissue measurement site.

44. The apparatus of Claim 41, wherein said calibration is developed using multivariate analytical techniques, and wherein said model implicitly incorporates said shift information in multivariate regression coefficients.

45. The apparatus of Claim 44, wherein said tissue state parameter is monitored by:

calculating an absorbance spectrum from said NIR spectrum;

optionally, pre-processing said absorbance spectrum; and

calculating a skin temperature value by applying said multivariate calibration model.

46. The apparatus of Claim 44, wherein said tissue state parameter is modified by applying one or both of said means of control so that skin temperature is restored to said target range.

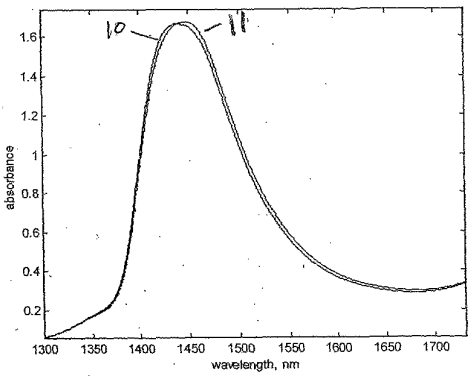

10
11
absorbance
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
1300
1350
1400
1450
1500
1550
1600
1650
1700
wavelength, nm

Fig. 1

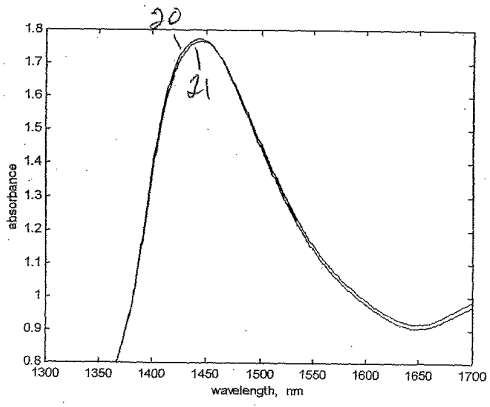

20
21
absorbance
wavelength, nm
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
1300
1350
1400
1450
1500
1550
1600
1650
1700

Fig. 2

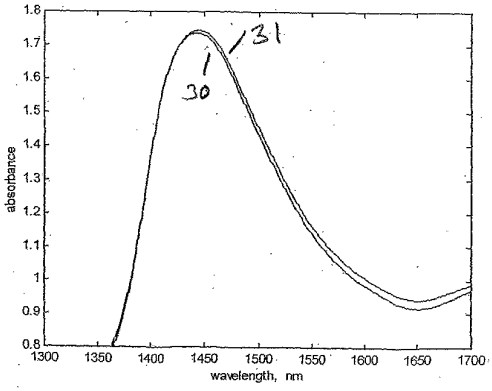

31
30
absorbance
wavelength, nm
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
1300
1350
1400
1450
1500
1550
1600
1650
1700

Fig. 3

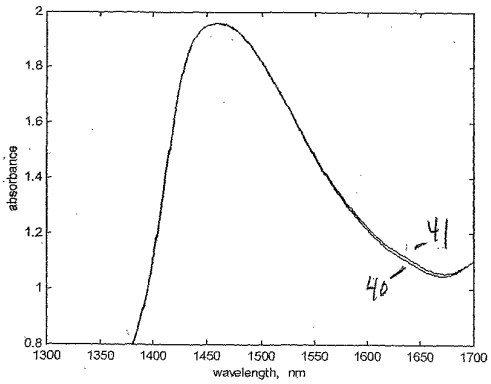

absorbance
wavelength, nm
41
40

Fig. 4

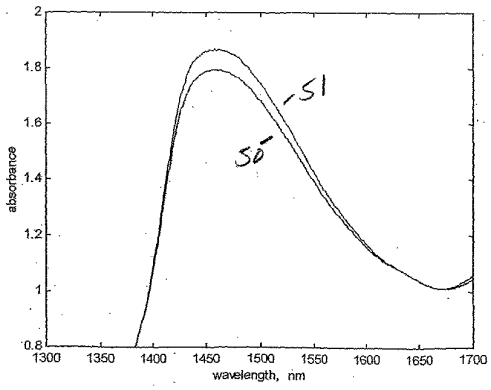

absorbance
wavelength, nm
51
50

Fig. 5

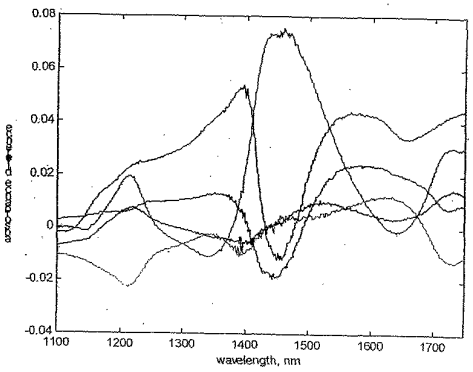

0.08
0.06
0.04
0.02
0
-0.02
-0.04
1100
1200
1300
1400
1500
1600
1700
wavelength, nm

Fig. 6

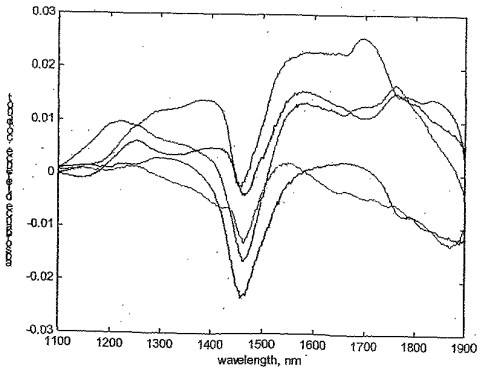

0.03
0.02
0.01
0
-0.01
-0.02
-0.03
1100
1200
1300
1400
1500
1600
1700
1800
1900
wavelength, nm

Fig. 7

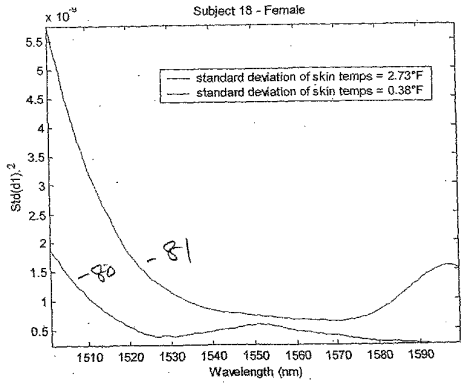

Subject 18 - Female
x 10^-4
standard deviation of skin temps = 2.73°F
standard deviation of skin temps = 0.38°F
Std(d1)^2
Wavelength (nm)
-80
-81

Figure 8

Fix w. grids

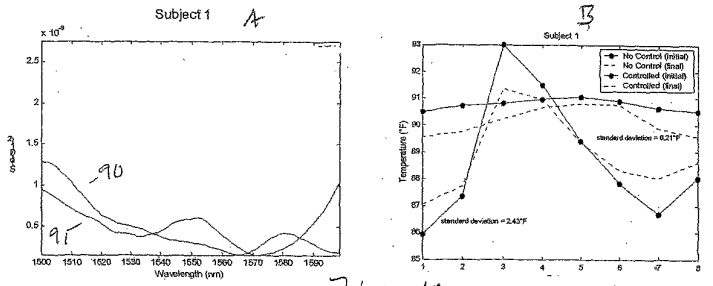


Figure 10

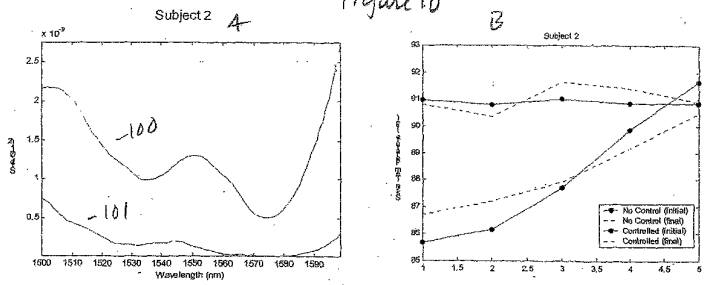
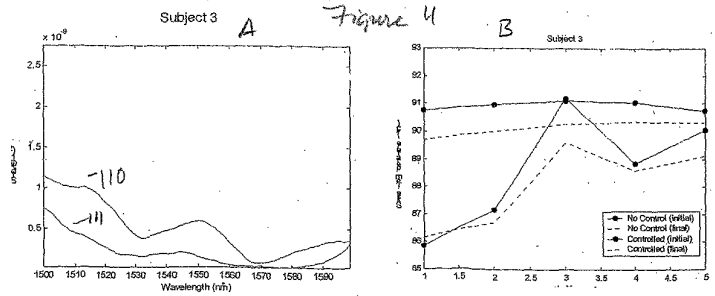


Figure 11



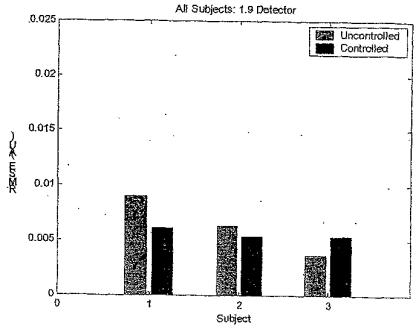


Figure 12

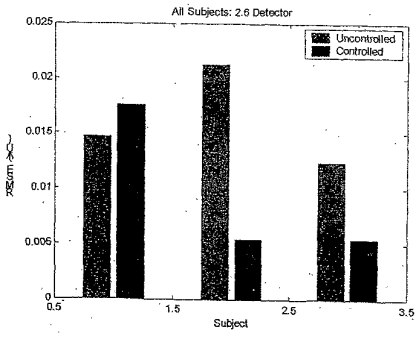


Figure 13

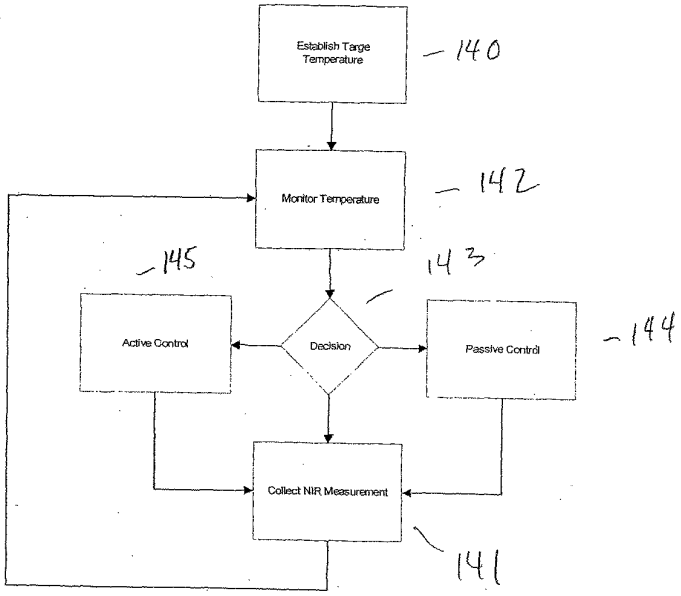

Establish Targe Temperature
140
Monitor Temperature
142
145
143
Active Control
Decision
Passive Control
144
Collect NIR Measurement
141

Figure 14

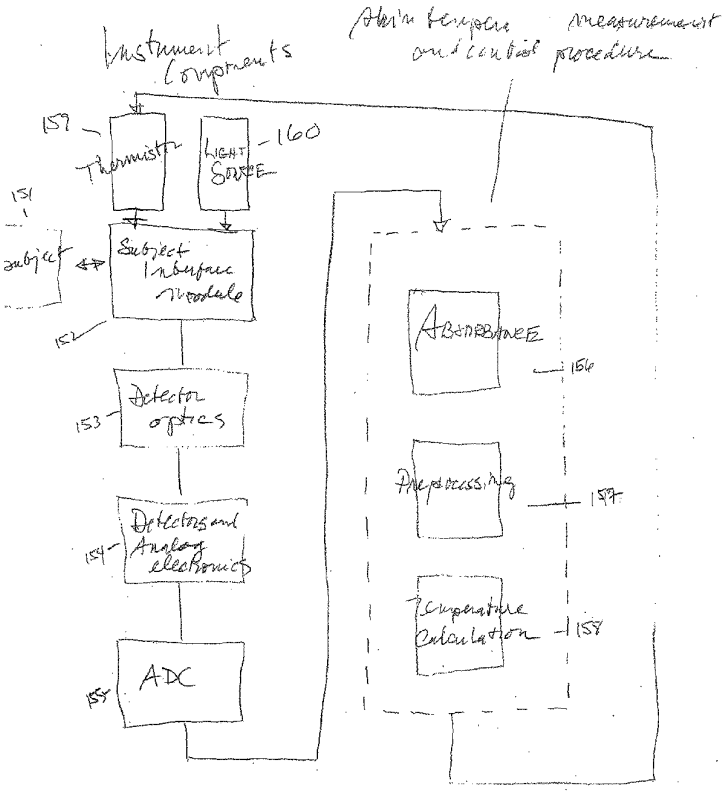

Instrument components
Alarm response and control procedure measurement
159
Thermistor
160
Light Source
151
subject
Subject Interface module
152
Detector optics
153
Detectors and Analog electronics
154
ADC
155
Absorbance
156
Preprocessing
157
Temperature Calculation
158

Figure 15

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09/955,531 17 September 2001 (17.09.2001) US

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(74) Agents: GLENN, Michael et al.; Glenn Patent Group, Ste. L, 3475 Edison Way, Menlo Park, CA 94025 (US).

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WO 02/026122 A1

(54) Title: MINIMIZING SPECTRAL EFFECTS DURING NIR-BASED BLOOD ANALYTE DETERMINATION

(57) Abstract: A method and apparatus for minimizing confounding effects in a noninvasive *in-vivo* spectral measurement caused by fluctuations in tissue state monitors a selected tissue state parameter within a target range, at which spectral effects attributable to the changes in the selected parameter are minimized. The invention includes means for both active and passive control in maintaining the selected tissue state parameter within the target range.

【国際公開パンフレット（コレクトバージョン）】

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(74) Agents: GLENN, Michael et al.; Glenn Patent Group, Ste. L., 3475 Edison Way, Menlo Park, CA 94025 (US).

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WO 02/026122 A1

(54) Title: MINIMIZING SPECTRAL EFFECTS DURING NIR-BASED BLOOD ANALYTE DETERMINATION

(57) Abstract: A method and apparatus for minimizing confounding effects in a noninvasive *in-vivo* spectral measurement caused by fluctuations in tissue state monitors a selected tissue state parameter within a target range, at which spectral effects attributable to the changes in the selected parameter are minimized. The invention includes means for both active and passive control in maintaining the selected tissue state parameter within the target range.

Minimizing Spectral Effects During NIR-Based Blood Analyte Determination

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The invention relates to the field of noninvasive tissue constituent analysis. More particularly, the invention relates to a method and apparatus for minimizing spectral effects in NIR spectral measurements for noninvasive blood analyte determination attributable to tissue state variations.

DESCRIPTION OF RELATED ART

Near infrared (NIR) tissue spectroscopy is a promising noninvasive technology that bases measurements on the irradiation of a tissue site with NIR energy in the 700-2500 nanometer wavelength range. The energy is focused onto an area of the skin and propagates according to the scattering and absorption properties of the skin tissue. Therefore, the reflected or transmitted energy that escapes and is detected provides information about the tissue volume that is encountered. Specifically, the attenuation of the light energy at each wavelength is a function of the structural properties and chemical composition of the tissue. Tissue layers, each containing a unique heterogeneous particulate distribution, affect light absorbance through scattering. Chemical components such as water, protein, fat and blood analytes absorb light proportionally to their concentration through unique

absorption profiles or signatures. The measurement of tissue properties, characteristics or composition is based on detecting the magnitude of light attenuation resulting from its respective scattering and/or absorption properties.

While noninvasive prediction of blood analytes, such as blood glucose concentration, has been pursued through NIR spectroscopy, fluctuations in tissue state, such as skin temperature, lead to increased spectral variance that can lead to a reduction of the net analyte signal, thus rendering it difficult to extract valuable analyte information.

Human tissue can consist of as much as 80% water, which has a known peak shift that is a function of temperature, in the NIR absorbance spectrum. As temperature increases, the water band shifts to shorter wavelengths as a result of a decrease in hydrogen bonding. As light irradiates the tissue and travels through the layers of the skin, it is scattered and absorbed by the constituents of the skin before exiting the skin, where it is detected by a spectrometer. Skin temperature variation is introduced into the spectral measurement in two ways. First, the resulting signal contains spectral information from the tissue volume it has traversed, including contributions from the natural temperature gradients present in the optical sampling path of human tissue. Second, human skin and sub dermal tissue undergo temperature variations, as a result of environmental and physiological factors, to maintain a uniform core body temperature. During the course of a day, skin temperatures have been observed to fluctuate by as much as 5° F in healthy individuals. These factors result in temperature variations between the

measurements comprising a data set. Therefore, water band shifts within a measurement and between measurements are present in the data set. The data set is used to estimate the analyte of interest through the development of a multivariate mathematical calibration model.

Within and between measurement temperature variations add a level of complexity to the multivariate analysis, making it more difficult to extract valuable analyte information. Large variations in temperature lead to increased spectral variance that can lead to a reduction of the net analyte signal. In addition, uncontrolled skin temperature variations have a higher probability of correlating with analytes of interest. Such chance correlations can lead to false calibrations, which may or may not be discernible.

Various spectroscopic methods and apparatuses that aim to monitor or alter sample temperature in some way are described in the prior art. For example, J. Braig, D. Goldberger, B. Sterling, *Self-emission noninvasive infrared spectrophotometer with body temperature compensation*, U.S. Patent No. 5,615,672 (April 1, 1997) describe a "self-emission" glucose monitor that noninvasively measures glucose concentration in a subject's blood by monitoring the infrared emission of glucose in the blood at long infrared wavelengths near 10 microns. The described device utilizes the infrared energy emitted by the person's blood and/or surrounding tissue to perform the absorption analysis. A temperature-sensing device for measuring the person's internal temperature at the arm is also used to adjust the constituent concentration measurement for temperature dependent effects. While the use of the person's own infrared energy, emitted as body heat, for an infrared

source eliminates the necessity of providing an energy source, the described device and the attendant method require a determination of the individual's internal temperature; however, the sensor measures temperature at the skin surface. Therefore, the calculated compensation for internal body temperature to be applied to the measured spectral signal introduces a significant source of error in the analyte concentration estimate. Additionally, the sensor's thermal time constant introduces an undesirable latency into the measurement, possibly as long as 1 1/2 minutes. Furthermore, the described device merely calculates a correction to be made to the spectral signal that compensates for the effect of the subject's body temperature. No provision is made for control of temperature within a target range in order to provide an optimal sample temperature, at which temperature-related spectral effects are minimized. Additionally, the Braig, *et al.* teachings are concerned with the mid- and far regions of the IR spectrum.

M. Block, *Non-invasive IR transmission measurement of analyte in the tympanic membrane*, U.S. Patent No. 6,002,953 (December 14, 1999) describes non-invasive methods and apparatuses for measurement of concentrations of selected blood constituent in which an optical device is inserted into the external ear canal to direct a portion of the electromagnetic radiation onto an IR detection and analysis device. The tympanic membrane is cooled to create a temperature differential with the inner ear, thus facilitating the emission of thermal radiation across the tympanic membrane. The insertion of an optical instrument deep into the ear canal and chilling of the tympanic membrane are by no means invasive, although they may be seen to be minimally invasive compared to more traumatic methods of

sampling, such as venipuncture. The Block teachings make no provision for spectroscopy-based measurement of temperature at the measurement site. The cooling of the tympanic membrane is not done to minimize spectral effects of tissue state fluctuation, but to facilitate thermal transfer. With the exception of cooling the tympanic membrane in a stereotypical fashion, the Block device is incapable of controlling temperature at the measurement site. The Block device further provides no closed loop in which spectroscopic temperature determinations provide the feedback required for control of site temperature.

J. Braig, C.Kramer, B. Sterling, D. Goldberger, P. Zheng, A. Shulenberger, R. Trebino, R. King, C. Barnes, *Method for determining analyte concentration using periodic temperature modulation and phase detection*, U.S. Patent No. 6,161,028 (December 12, 2000) describe a method of determining the analyte concentration of a test sample that employs a rationale similar to that of Block. A temperature gradient is introduced in the test sample and infrared radiation detectors measure radiation at selected analyte absorbance peak and reference wavelengths. The Braig, *et al.* teachings employ gradient spectroscopy, in which a temperature gradient is produced in the sample to facilitate thermal transfer, thereby delivering more thermal radiation to the radiation detectors. The method described does not address the problem of spectral effects related to fluctuations in tissue state at the measurement site and their confounding effect on the net analyte signal. With the exception of inducing a temperature gradient in the sample, the described method provides no way of controlling sample temperature within a target range that minimizes the spectral effects caused by fluctuations in sample temperature.

In view of the problems left unsolved by the prior art, there exists a need for a way to control spectral effects attributable to tissue state variations, such as skin temperature, during NIR-based, non-invasive blood analyte determination, by monitoring the selected tissue state parameter and maintaining it within a predetermined target range of values at which such spectral effects are minimized. It would be a significant technological advance to monitor the tissue state parameter spectroscopically, in which a calibration model calculates measured values by correlating shifts in the selected tissue state parameter with shifts in observed spectral effects, thus eliminating the time constants imposed by conventional sensor devices. It would be desirable to provide a means of controlling the selected tissue state parameter, driven by a closed loop, in which the calculated values provided the feedback for determining the degree of control to be applied.

SUMMARY OF THE INVENTION

The invention provides a method and apparatus for minimizing confounding effects in a noninvasive *in-vivo* spectral measurement caused by fluctuations in tissue state. A selected tissue state parameter is spectroscopically monitored through the application of a multivariate calibration model that correlates spectroscopic changes with fluctuations in the selected tissue state parameter, providing near-instantaneous measurements, without the imposition of any significant time constants. A target range of values for the selected parameter is empirically determined from an experimental data set

by observing the spectra of the data set to determine a range of values at which spectral effects due attributable to the changes in the selected parameter are minimized. During measurement, the selected parameter is continuously monitored. The calculated values provide feedback in a closed loop that drives a device for maintaining the selected tissue state parameter within the target range. Means for both active and passive control of the tissue state parameter are included in the invention.

A preferred embodiment of the invention provides a method and apparatus for minimizing the confounding effects in a noninvasive near IR spectral measurement attributable to shifts in skin temperature at the tissue measurement site. Skin temperature at the measurement site is spectroscopically monitored by calculating temperature values through the application of a multivariate calibration model that correlates spectroscopic changes with shifts in skin temperature. Thermal time constants imposed by conventional temperature sensing devices are eliminated, providing near-instantaneous temperature readings. Active and passive control means are provided. Passive control is achieved through the selective application and removal of an occlusive thermal wrap. Active control is provided by a thermistor applied to the skin in the vicinity of the measurement site. Active and passive control may be applied in complementary fashion or they may be used separately. In a particularly preferred embodiment of the invention, the control means is incorporated into the measurement instrument, wherein the calculated skin temperature values provide the feedback in a closed loop that drives the control device. In an alternate embodiment of the invention, the temperature values are supplied to an operator, who then applies active

and/or passive control to achieve and maintain a skin temperature within the target range. By monitoring skin temperature spectroscopically and employing methods of passive and/or active control it is possible to reduce the effects of skin temperature variation on the NIR measurement. The invention finds particular application in the noninvasive measurement of blood glucose concentration.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides absorbance spectra, showing a water absorbance peak, measured at two different temperatures;

Figures 2 and 3 provide absorbance spectra, showing a water absorbance peak, of two different subjects measured on a spectrometer instrument having a fiber optic subject interface, according to the invention;

Figures 4 and 5 provide absorbance spectra of the subjects of Figures 2 and 3, measured on a spectrometer instrument having a subject interface constructed from lenses, according to the invention;

Figure 6 shows difference spectra for the absorbance spectra of Figures 2 and 3, according to the invention;

Figure 7 shows difference spectra for the absorbance spectra of Figures 4 and 5, according to the invention;

Figure 8 presents a plot of spectral variance versus wavelength for a diabetic test subject, according to the invention;

Figures 9a through 11a provide plots of spectral variance versus wavelength for three healthy subjects, according to the invention;

Figures 9b through 11b provide plots of minimized and large temperature variation for the three subjects of Figures 9a – 11a, according to the invention;

Figures 12 and 13 provide bar graphs of between sample variation relative to two different LED detectors for the three subjects of Figures 9 –11, according to the invention;

Figure 14 provides a block diagram of a method for measuring and controlling skin temperature at a tissue measurement site, according to the invention; and

Figure 15 provides a block diagram of a spectrometer instrument for measuring and controlling skin temperature at a tissue measurement site, according to the invention.

DETAILED DESCRIPTION

Skin Temperature Measurement and Control Using NIR Spectroscopy

Near Infrared measurements of skin combined with associated skin temperature reference measurements are used to develop NIR temperature calibrations that require only NIR tissue scans to predict skin surface temperature. Methods of developing calibrations for spectral analysis may employ a variety of multivariate analytical techniques that are well known to those skilled in the art. NIR skin temperature calibration is made possible by the known shifting of the 1450 nm water band with variations in skin temperature. The calibration model incorporates the shift information implicitly in the multivariate regression coefficients. Temperature measurement and control of human tissue is important in noninvasive NIR measurement because it provides a means of simplifying the complex overlapping spectral effects that inhibit extraction of the analyte signal. The extra temperature measurement hardware and the associated cost and complexity are avoided by using NIR temperature measurement.

An advantage of the NIR measurement over the primary thermistor measurement lies in the absence of thermal time constant inherent in conventional sensing hardware. Measured skin thermistor response frequently requires as much as 1 1/2 minutes to reflect 95% of the sample temperature change under a step change of 10° F. Eliminating the time constant in the temperature measurement provides significant advantages in the implementation of active closed-loop temperature control of the skin by providing near-immediate skin temperature feedback unimpeded by the time constant inherent in primary measurement methods.

Skin temperature calibrations for multiple individuals have been established using the calibration data from a single subject. This result foretells the feasibility of general skin temperature calibrations that can be established on site prior to the shipment of the instrument.

Procedures for active and passive control of skin temperature are provided below. Near infrared (NIR) tissue spectroscopy is utilized to irradiate the skin and estimate biological analytes of human subjects. Skin temperature variation is destructive to the NIR measurement in two ways: First, false calibrations can occur if skin temperature correlates to analytes of interest, and second, large skin temperature fluctuations decrease the net analyte signal. An apparatus and procedure to passively and actively control skin temperature to prevent decreasing the net analyte signal and spurious correlations is described. The procedure for controlling skin temperature involves determining the target skin temperature, monitoring the actual skin temperature, and applying passive and/or active control methods to attain the target temperature.

Experiments were conducted to:

- Characterize the effects of skin temperature variation on the NIR spectrum – see Experiments I and II, below.
- Characterize skin temperature profiles over the course of a day and between days, and to determine target temperatures – see Experiment II and III, below.
- Test methods of controlling skin temperature to within ± 1° F – see Experiment III, below.

Methods of Skin Temperature Control

One of the primary functions of the skin is to maintain a constant body temperature. Physiological responses to external and internal stimuli can limit skin temperature control. Periodic monitoring is a critical step in achieving good temperature control. Using the invention, the skilled practitioner is enabled to discern trends in skin temperature and implement passive and/or active control as compensation, thus maintaining a stabilized skin temperature at the spectral measurement site.

Skin temperature is monitored using a temperature probe attached to the skin within 5 mm of the spectral measurement site. As the discussion of Experiment II, below shows, daily skin temperature profiles have shown that temperatures are generally lower in the morning and gradually increase throughout the day, resulting in a profile with a gentle positive slope that stabilizes with time. As indicated in the discussion of Experiment III, below, healthy and diabetic skin temperature profiles have resulted in an initial target skin temperature range of 90-92° F, representative of temperatures observed in the mid- to late afternoon. Target ranges may vary depending on the individual. The following methods are utilized to achieve and maintain the target range:

PASSIVE CONTROL

Passive control, by means of a thermal wrap placed around the subject's forearm, can be implemented to quickly drive the skin temperature to the target temperature in the morning. This results in a profile with a steep positive slope during the first hour, followed by more uniform skin temperatures during the rest of the day. The wrap covers the forearm from the wrist to elbow and, therefore raises the temperature of the entire forearm. The wrap can be adjusted loosely or snuggly around the subjects arm, or removed, as needed to maintain the skin temperature within the target range.

ACTIVE CONTROL

Active control utilizes a temperature-controlled copper heat sink to rapidly change the temperature of the skin. The set point of the heat sink can be adjusted to warm or cool the skin. Active control is localized to the skin that comes into contact with the heat sink, which has the same dimensions as the subject-spectrometer interface. If the skin temperature is significantly outside of the target range just prior to the spectral measurement, the arm is placed on the heat sink for 1-2 minutes before the measurement.

The methods presented above can be used in a complementary fashion to maintain skin temperature within the target range. The method chosen is a function of the time available before the spectral measurement and observed skin temperature. The decision to implement active or passive control is made each time the skin temperature is monitored based upon the time available before the spectral measurement and the difference between the actual and target temperatures. Passive control is best suited for time periods greater

than 1-2 minutes, whereas active control is advantageous if rapid temperature increases or decreases are required. A flow diagram of a general procedure to control skin temperature is presented in Figure 14. As described herein, a target temperature is established 140 empirically by observing spectral measurements and establishing a target range at which spectral variation is kept to a minimum. NIR spectral measurements are collected 141, and skin temperature is monitored 142 spectroscopically by the application of a multivariate calibration to the spectral measurement that correlates spectral effects with skin temperature. The temperature reading is evaluated 143. If skin temperature is within the target range, no control is implemented. If the skin temperature is outside of the target range, either passive 144 or active 145 control, or a combination of both, are implemented to bring temperature back into the target range. It can be seen from Figure 14 and 15 that the system of the current invention represents a closed loop, in which the control devices are driven by the feedback supplied by the spectroscopic temperature determinations.

A spectrometer instrument for implementing the invented method is shown in Figure 15. A subject interface module 152 is coupled with a tissue measurement site on the skin of the subject 151. A thermistor 159 mounted within the subject interface module has a set point within the target range. In order to maintain its set point, the thermistor either heats or cools the skin surface. In a preferred embodiment of the invention, the subject interface module comprises a fiber optic probe. The subject interface module directs light emitted from the light source 160 toward the tissue measurement site. Light that is back diffused form the tissue measurement site is directed toward

one or more photo detectors 154 by detector optics 153, in this case, a fiber optic. Analog electronics convert the detected light to a voltage, which is subsequently converted to a digital value by an analog-to-digital converter (ADC) 155. From these digital values, an absorbance spectrum is calculated 156. The absorbance spectrum may be subjected to one or more of the pre-processing techniques 157 previously described. Subsequently, a temperature value is calculated 158 from the absorbance spectrum through the application of the calibration model previously described. Finally, the calculated temperature value is routed to a controller (not shown) that interfaces with the thermistor 159, to provide temperature feedback.

EXPERIMENT I: Impact of Skin Temperature on NIR Spectra

SUMMARY

A preliminary study was conducted in order to determine if the optical configuration of the FOCSI (fiber optic coupled scanning instrument) spectrometer instrument, supplied by Instrumentation Metrics, Inc., Tempe AZ, was superior to the optical configuration of the DRACO spectrometer instrument, also supplied by Instrumentation Metrics, Inc. with respect to the information content contained in the water band of the NIR spectrum. The water band at 1450 nm is known to shift with sample temperature, rendering the modeling of glucose in water and tissue more difficult over samples that are taken at widely varying temperatures. Therefore, a blood glucose prediction algorithm must incorporate a calibration strategy that utilizes the shift in the water band to simplify the modeling challenges. Thus, an optical

design that permits evaluation of tissue temperature information is an important design criterion for a noninvasive glucose monitor. In this study, it was observed that noninvasive measurements taken at different temperatures on the FOCSI instrument were substantially more consistent with the expected spectral behavior than those taken on the DRACO. It is suspected that the highly variable sample pathlength inherent in the noninvasive DRACO measurement confounds the interpretation of temperature effects.

INTRODUCTION

Water, comprising as much as 80% of human tissue, has a known peak shift in the NIR absorbance spectrum with increasing sample temperature. The shift of the water band to shorter wavelength arises as a result of the increased solution pH and a concomitant decrease in hydrogen bonding with increasing temperature. In Figure 1, the transmission spectrum of the first-overtone band of water is plotted at 33 (11) and 41 (10) degrees centigrade. An *in vivo* measurement peak can be expected to contain spectral contributions from a distribution of temperature states due to a natural temperature gradient present in the optical sampling path of human tissue. Modeling glucose in this thermally complex sample matrix is one of the more significant challenges of *in vivo* measurement using NIR spectroscopy. Accurate compensation for tissue temperature is best approached by inference from the spectral measurement because probing tissue with near infrared light is likely to lead to localized effects on the surface and in the tissue. A temperature probe cannot be inserted into the light path of the spectrometer without disturbing the measurement and a non-invasive temperature probe will not account for temperature gradients in tissue. The

most effective means of compensating for tissue temperature variation requires that the measured spectrum contain substantive information about the position and shape of the water band. The shape of the water band is also influenced by tissue optics, making the acquisition of highly informative spectral scans even more important. In light of these considerations, instrumental or sampling artifacts that distort the shape of the water band are highly undesirable and should strongly influence the design of non-invasive glucose instrumentation based on NIR spectroscopy.

EXPERIMENTAL

Six subjects were scanned on both the FOCSI and DRACO scanning spectrometers. Two sets of experiments were conducted on each subject. In the first experiment, the subject was scanned at normal ambient skin temperature, while the second experiment was conducted after preheating subjects' skin temperature to 3-5° F above the normal skin temperature. Measurements taken prior to the study led to the establishment of the following protocols for spectrum measurement: Rapid temperature and physiological changes were reduced by allowing 3 minutes of arm contact with the instrument subject interface module prior to the acquisition of spectra. A YSI 4000 skin temperature sensor, supplied by YSI, Inc., Yellow Springs OH, with a readout to ±0.05° F was placed about 5mm from the measurement site during the course of the experiments. Temperature was recorded every 30 seconds and scans were conducted over a period of two minutes. Reference spectra using an 80% reflectance standard were acquired directly before and after the *in vivo* measurement.

RESULTS AND DISCUSSION

Scans taken on each spectrometer instrument were examined for temperature related effects for each of the six subjects. Temperature related effects that are consistent with a change in the temperature distribution of sample tissue were noted in three of the four remaining patients scanned on the FOCSI, but temperature related effects were not as obvious in the scans taken on the DRACO. In Figures 2 and 3, the scans taken on the FOCSI from two individuals at two temperature levels are plotted. One set of spectra were taken at skin temperatures 5° F (21, 30) higher than the other (21, 31). It is evident that the higher temperature scans had greater difference in intensity between the 1450 nm maximum and the minimum absorbance at 1650-1700 nm. The edge of the high temperature spectrum peak is also on the inside of the low temperature spectrum on the long wavelength side of the 1450 nm water band. These spectral differences are consistent with the existence of a more narrow range of water temperatures in the heated tissue, giving rise to a sharper peak. According to scattering theory, the scattering of tissue increases with temperature. The spectral region with the most dominant scattering effects is in the short wavelength region around the second-overtone band at 1100-1300 nm. Scattering is believed to diminish rapidly after the second overtone region. Suppression in the sample absorbance with increasing temperature is consistent with the expected optical behavior of tissue. The absorbance decrease from increased scattering with temperature is pronounced at the second overtone, but it may also be significant at the first overtone on highly absorbed spectral features like the maximum of the water band.

The corresponding scans 40, 50 and 41, 51 taken on the DRACO are plotted in Figures 4 and 5. As previously mentioned, temperature effects are not nearly as noticeable as they are in the spectra of Figures 2 and 3. Difference spectra calculated using the individual subject spectra taken at cool and warm skin temperatures should contain spectral information related to temperature changes in the tissue. A consistent measurement should yield difference spectra of similar shape for each of the individual test subjects. The spectra acquired for each subject at cool and warm skin temperature were subtracted and the resulting difference spectra for the DRACO spectrometer are plotted in Figure 6 and those for the FOCSI instrument are plotted in Figure 7. Clearly the difference spectra (Cold minus hot) are more consistent in shape for the FOCSI experiments than for the measurements taken with the DRACO. The temperature-induced scattering effects around the second-overtone region are consistent with scattering research for the FOCSI in that the cold minus the hot spectrum consistently yielded the positive residual expected from increased scattering by tissue at elevated temperature. It is obvious from Figures 6 and 7 that interpretations of measurements on tissue at normal and warmed temperature states using the DRACO optical system were not as simple as the corresponding measurements taken on the FOCSI. The DRACO optical system may be more susceptible to variations in tissue sampling and surface reflection that may arise due to sensor positioning and pressure.

Conclusions

The temperature studies conducted here can be used to confirm that the

FOCSI subject interface module was more effective than the DRACO subject interface module for collection and identification of temperature-related variation present in *in vivo* spectral measurements. Differences in the spectra of normal and heated tissue were on the order of several hundredths of an absorbance unit, making the noise disadvantage of the DRACO detectors a non-issue in these comparisons. The greatest remaining difference between the units was in the optical sampling systems: The DRACO with a conventional lens system and the FOCSI with a fiber optic light transport system running from the monochromator to the sample and back to the detectors. The presence of a significant level of variable skin surface reflectance and a wider optical path distribution inherent to the DRACO measurements was expected to lead to broadening and shape uncertainty in the water band at 1450 nm. See J.D. Hardy, H.T. Hammel, D. Murgatroyd, J Appl. Physiol., 9:257(1956). Alternately, the FOCSI system was expected to have a negligible surface reflectance component and a more narrow distribution of sample pathlengths for photons that reach the instrument detectors. These optical differences between the DRACO and the FOCSI were expected to contribute to lower information content in the water band measured by the DRACO. Additionally, other, less obvious factors would significantly limit or enhance the interpretation of temperature related spectral variation.

It was encouraging that temperature related spectral variation of scans taken on the FOCSI was consistent with the expected spectral shift and optical scattering properties of water and human tissue. Significantly, experiments on the DRACO were not as successful at producing systematic spectral variation

with skin temperature. The most likely source of the measurement inconsistency of scans taken on the DRACO is the sample-to-sample variation in skin surface reflectance. Unfortunately, even modest changes in surface reflectance between different measurements of the same subject can lead to changes in the amplitude and shape of the water band, which in turn make the interpretation of temperature-related spectral variation difficult or impossible. *In vivo* sample scattering and the related changes in mean optical path can vary with changes in temperature, pressure, physiological response, and sampling location. Compensation for temperature requires that temperature-related variation could be largely separated from these other effects. Resolution of skin temperature states is made substantially more challenging on the DRACO instrument because the spectral variation due to factors other than temperature is larger than for the FOCSI instrument. The consistency of the measurements taken in this experiment and the resulting information content lead to the conclusion that a fiber-based instrument is preferred for use in compensation of temperature-related spectral variation.

EXPERIMENT II: Skin Temperature Profiles

SUMMARY

The objective of the current study was to characterize skin temperature profiles, both uncontrolled and with passive skin temperature control. Both uncontrolled and passively controlled skin temperatures were found to be lowest early in the day, with a tendency to stabilize as the day progressed. The passively controlled and the uncontrolled profiles tended to track each

other, although passively controlled skin temperature were less susceptible to sudden changes.

EXPERIMENTAL

Eight subjects were divided into two groups, each group including three males and one female. Both uncontrolled and passively controlled skin temperature profiles were collected on an hourly basis between 9AM and 6PM for three days. For group one, skin temperature was passively controlled by occluding a measurement site on the forearm with a THERMAX wrap. For group two, passive control was by means of the THERMAX wrap on day one. On days two and three, control was by means of a fleece arm sleeve that covered the entire forearm. For both groups, the uncontrolled temperature measurements were collected on the subjects' other forearms, which were left unoccluded. Skin temperature determinations were made using a YSI 4000 temperature sensor.

RESULTS AND DISCUSSION

It was observed that initial temperature was dependent on subjects' clothing: subjects wearing long sleeves had higher initial temperatures. All eight subjects were right-handed, and it was observed that right arm temperatures were generally higher. Subjects' arm temperatures did not necessarily correlate with room temperature; typically arm temperature rose steeply in the morning, then it either stabilized and eventually dropped, or continued to rise in a more gradual fashion than the initial steep rise. The day-to-day highest

temperature in the passive controls occurred in a relatively narrow range of 91-93° F for seven of the eight subjects. Day-to-day lowest temperature was highly variable and may have been affected by ingestion of stimulant beverages such as coffee and soft drinks. Passively controlled skin temperatures were generally less susceptible to sudden changes in temperature of the external environment, such as when the subject went outside. After the initial AM rapid temperature increase, the controlled and the uncontrolled profiles tended to track each other, with the spread between uncontrolled and controlled temperatures remaining fairly constant. This may have been a result of a sympathetic response that tended to stabilize temperatures between the uncontrolled arm and the controlled arm. Finally, it was observed that skin temperature could by increased approximately 2-9° F by covering the entire forearm with the fleece arm sleeve.

CONCLUSIONS

Skin temperature is subject to a number of environmental and physiologic influences. The use of various passive control strategies can minimize skin temperature fluctuations to such a degree that a range of ± 1° F may be maintained. Application of passive temperature controls can precipitate rapid increases in skin temperatures.

EXPERIMENT III: Preliminary effects of skin temperature on sample repeatability

SUMMARY

The current studies focus on the relationship between skin temperatures and noninvasive spectra, in particular, how large skin temperature excursions impact sampling precision. A study was conducted in which noninvasive spectra were collected over a large range of skin temperatures as well as over a controlled range of skin temperatures for each of three subjects. Preliminary results indicate that minimal skin temperature variation leads to a reduction of the spectral variance in the 1500-1600 nm wavelength region.

INTRODUCTION

Skin temperature data from a first pool of diabetic test subjects undergoing repeated oral glucose tolerance tests over several visits show that any given subject may exhibit large skin temperature variations between visits as well as over the course of a single visit of four hours' duration. These variations may result from several factors, including environmental and physiological conditions. It is necessary to understand the impact of large temperature variations on between sample stability. Monitoring skin temperature in a second pool of healthy individuals revealed that temperatures vary as much as 5° F in the course of a typical workday. A study was conducted to generate two sets of data for each of three participants. The first data set contained noninvasive samples with large skin temperature excursions of up to approximately 8° F between samples, while the second data set consisted of samples that were controlled within a 2° F range.

EXPERIMENTAL PROCEDURE

Three subjects, 2 males and 1 female, participated in the second study. Prior to measurement, the measurement site was occluded with a plug of RTV (room temperature vulcanizing) silicone rubber for forty-five minutes. A FOCSI 9 (fiber optic coupled scanning instrument) spectrometer instrument, manufactured by Instrumentation Metrics, Inc. of Tempe AZ was employed to collect all data. An optical coupling fluid, FLUORINERT FC-40, supplied by 3M Corporation, St. Paul MN, was employed to enhance coupling between the measurement site and the fiber optic probe of the spectrometer. A reference scan (80% reflectance standard) and a polystyrene scan were collected with each sample. YSI temperature probes, supplied by YSI, Inc. of Yellow Springs OH were used to record skin temperature measurements near the spectral measurement site.

Five to eight samples were collected for both large and minimized skin temperature variation. Minimized skin temperature variation, herein referred to as controlled samples, was achieved by passively warming the measurement arm to approximately 91° F with a small blanket. Uncontrolled samples, having large temperature variations, consisted of samples with skin temperatures varying from approximately 86° to 93° F.

DATA ANALYSIS

Preprocessing steps, including baseline correction, x-axis standardization, outlier detection, and conversion to absorbance were applied to the data set prior to analysis. Each sample, consisting of 16 raster scans was ensemble

averaged. First derivative spectra were obtained using a thirty-five point first order Savitsky-Golay filter. The square of the standard deviation of each set of samples was calculated and is referred to as the spectral variance. The smaller the spectral variance, the simpler the matrix is for PLS (partial least squares) modeling.

In addition, RMSE (root mean square error) values were calculated to assess the sampling repeatability for controlled and uncontrolled samples. The entire usable wavelength regions for each detector (1100-1700 nm and 1400-2400 nm for the 1.9 μm and 2.6 μm detectors, respectively) were used to determine these values.

RESULTS

Figure 8 presents the spectral variance versus wavelength for clinic data for an exemplary subject from the first subject pool. The data includes samples from two separate clinic visits. Samples were separated according to skin temperature. The standard deviations of the skin temperatures were 0.38° F (80) and 2.73° (81) F. When the skin temperature variations are small, spectral variance in the 1500-1600 nm spectral region is observed to be noticeably reduced.

The study involving the second subject pool also indicates that minimization of skin temperature variation leads to reduced spectral variance. Figures 9 –11 through present the spectral variance for the 1.9 μm detector versus wavelength for subjects 1 through 3. Figures 9a –11a provide plots of spectral variance for standard deviation of skin temperatures equal to 2.73° F (90, 100,

110) and .38° F (91, 101, 111) respectively, along with corresponding controlled and uncontrolled temperature profiles in Figure 9b-11b. Results are similar for the 1500-1600 nm region of the 2.6-μm detector. RMSE values are given in Figures 12 and 13, which indicate between sample repeatability of the data. Between-sample variation was moderately reduced on the 1.9-μm detector for subjects 1 and 2 and greatly reduced on the 2.6-μm detector for subjects 2 and 3 when temperature variation was controlled.

Both studies presented above suggest that samples with smaller variations in skin temperature result in reduced spectral variance in the wavelength region of interest.

In addition to skin temperature varying over time in a single individual, skin temperature ranges vary between individuals. For example, ambient temperature, time of day, physiological response to contact with the subject interface module of the instrument, the type of clothing and activity level all impact a person's skin temperature. Due to the large number of parameters involved, it is not feasible to define a single skin temperature at which noninvasive spectra should be collected. However, it is clear, that a method of minimizing skin temperature variation within a subject be reduces spectral variation within the wavelength region of interest. To minimize spectral variation, skin temperatures may be maintained at approximately 89-91° F. Wrapping the forearm with a blanket or other thermal wrapping is an effective method of raising the skin temperature prior to scanning and does not introduce large temperature transients during scanning. Another possible method of controlling skin temperature involves placing the arm on a

temperature-controlled heat sink prior to scanning.

While the invention has been described herein with respect to control of skin temperature, the invention may also be applied to other tissue state parameters such as hydration or surface pH. Additionally, while the invention finds particular application in noninvasive blood glucose determination, the invention also is applicable to the measurement of other constituents of blood and tissue; for example, cholesterol, other lipids, BUN, and protein. Furthermore, the invention would be suitable for the detection of foreign substances in the blood such as ethanol and various other drugs and toxins.

Although the invention has been described herein with reference to certain preferred embodiments, one skilled in the art will readily appreciate that other applications may be substituted without departing from the spirit and scope of the present invention. Accordingly, the invention should only be limited by the Claims included below.

CLAIMS

What is claimed is:

1. A method for controlling spectral effects attributable to tissue state variations during NIR-based, non-invasive blood analyte determination, comprising the steps of:

determining a target range of values for a selected tissue state parameter;

providing means for modifying said tissue state parameter;

providing a calibration model that correlates said spectral effects to variations in said tissue state parameter;

monitoring said tissue state parameter by measuring an NIR spectrum and calculating values for said parameter from said spectrum according to said calibration model; and

if said calculated value is outside of said target range, modifying said tissue state parameter until a measured value for said parameter is within said target range.

2. The method of Claim 1, wherein said tissue state parameter comprises skin temperature in the vicinity of a tissue measurement site on a body part of a live subject.

3. The method of Claim 2, said spectral effects comprising shifts in a peak water absorbance band in an NIR spectrum, wherein said peak water absorbance band shifts to shorter wavelengths as skin temperature increases

and wherein said peak water absorbance band shifts to longer wavelengths as skin temperature decreases;

wherein said shifts attenuate a net analyte signal.

4. The method of Claim 3, wherein said peak water absorbance band occurs in a wavelength region at approximately 1450 nm.

5. The method of Claim 3, wherein said target range comprises a range of skin temperatures wherein said shifts are minimized, so that said attenuation of said net analyte signal is minimized.

6. The method of Claim 5, wherein said target range is approximately eight-nine to ninety one degrees, Fahrenheit.

7. The method of Claim 3, wherein said step of determining a target range comprises:

empirically determining said target range by examining spectra from a calibration data set to determine a temperature range in which said shifts are minimized.

8. The method of Claim 2, wherein said means for modifying a tissue state parameter comprises one or both of:

means for actively controlling said skin temperature; and

means for passively controlling said skin temperature.

9. The method of Claim 8, wherein said active means and said passive means are employed in complementary fashion to maintain skin within said target range.

10. The method of Claim 9, wherein said active means of control is employed to induce rapid changes in skin temperature.

11. The method of Claim 8, wherein said passive means of control is employed for relatively longer time periods.

12. The method of Claim 8, wherein said means for passively controlling said skin temperature comprises a thermal wrap applied to said body part, wherein initial application of said thermal wrap causes a rise in skin temperature.

13. The method of Claim 12, wherein skin temperature is maintained within said target range by one of loosening, tightening and removing said thermal wrap.

14. The method of Claim 8, wherein said means for actively controlling said skin temperature comprises a temperature-controlled heat sink.

15. The method of Claim 14, wherein said heat sink has a set point within said target range, and wherein said heat sink cools or warms said skin to maintain skin temperature within said target range.

16. The method of Claim 14, wherein active control is localized to skin that comes into contact with said heat sink.

17. The method of Claim 3, wherein said step of providing said calibration model comprises developing said calibration model using a calibration data set that includes spectral measurements on a group of exemplary subjects combined with associated skin temperature reference measurements.

18. The method of Claim 17, wherein said reference measurements span a range approximately equal to or greater than said target range.

19. The method of Claim 17, wherein said reference measurements are made using a noninvasive temperature sensor placed in the immediate vicinity of the tissue measurement site.

20. The method of Claim 17, wherein said calibration is developed using multivariate analytical techniques, and wherein said model implicitly incorporates said shift information in multivariate regression coefficients.

21. The method of Claim 20, wherein said step of monitoring said tissue state parameter comprises the steps of:

calculating an absorbance spectrum from said NIR spectrum;

optionally, pre-processing said absorbance spectrum; and

calculating a skin temperature value by applying said multivariate calibration model.

22. The method of Claim 21, wherein said step of modifying said tissue state parameter comprises applying said means of control so that skin temperature is restored to said target range.

23. An apparatus for controlling spectral effects attributable to tissue state variations during NIR-based, non-invasive blood analyte determination, comprising:

means for modifying a selected tissue state parameter;

means for measuring an NIR spectrum at a tissue measurement site;

a calibration model that correlates said spectral effects to variations in said tissue state parameter;

means for monitoring said tissue state parameter by measuring an NIR spectrum and calculating values for said parameter from said spectrum according to said calibration model;

wherein said tissue state parameter is modified by said modifying means if said calculated value is outside of a target range until said parameter is within said target range.

24. The apparatus of Claim 23, wherein said tissue state parameter comprises skin temperature in the vicinity of a tissue measurement site on a body part of a live subject.

25. The apparatus of Claim 24, said spectral effects comprising shifts in a peak water absorbance band in an NIR spectrum, wherein said peak water absorbance band shifts to shorter wavelengths as skin temperature increases

and wherein said peak water absorbance band shifts to longer wavelengths as skin temperature decreases;

wherein said shifts attenuate a net analyte signal.

26. The apparatus of Claim 25, wherein said peak water absorbance band occurs in a wavelength region at approximately 1450 nm.

27. The apparatus of Claim 25, wherein said target range comprises a range of skin temperatures wherein said shifts are minimized, so that said attenuation of said net analyte signal is minimized.

28. The apparatus of Claim 27, wherein said target range is approximately eight-nine to ninety one degrees, Fahrenheit.

29. The apparatus of Claim 25, wherein target range is empirically determined by examining spectra from a calibration data set to determine a temperature range in which said shifts are minimized.

30. The apparatus of Claim 24, wherein said means for modifying a tissue state parameter comprises one or both of:

means for actively controlling said skin temperature; and

means for passively controlling said skin temperature.

31. The apparatus of Claim 30, wherein said active means and said passive means are employed in complementary fashion to maintain skin within said target range.

32. The apparatus of Claim 31, wherein said active means of control is employed to induce rapid changes in skin temperature.

33. The apparatus of Claim 30, wherein said passive means of control is employed for relatively longer time periods.

34. The apparatus of Claim 30, wherein said means for passively controlling said skin temperature comprises a thermal wrap applied to said body part, wherein initial application of said thermal wrap causes a rise in skin temperature.

35. The apparatus of Claim 34, wherein skin temperature is maintained within said target range by one of loosening, tightening and removing said thermal wrap.

36. The apparatus of Claim 30, wherein said means for measuring an NIR spectrum comprises a NIR spectrometer instrument, wherein said spectrometer instrument includes a subject interface module

37. The apparatus of Claim 36, wherein said means for actively controlling said skin temperature comprises a temperature-controlled heat sink.

38. The apparatus of Claim 36, wherein said heat sink is incorporated into said subject interface module, so that said heat sink is in contact with said tissue measurement site during use.

39. The apparatus of Claim 37, wherein said heat sink has a set point within said target range, and wherein said heat sink cools or warms said skin to maintain skin temperature within said target range.

40. The apparatus of Claim 37, wherein active control is localized to skin that comes into contact with said heat sink.

41. The apparatus of Claim 25, wherein said calibration model is developed using a calibration data set that includes spectral measurements on a group of exemplary subjects combined with associated skin temperature reference measurements.

42. The apparatus of Claim 41, wherein said reference measurements span a range approximately equal to or greater than said target range.

43. The apparatus of Claim 41, wherein said reference measurements are made using a noninvasive temperature sensor placed in the immediate vicinity of the tissue measurement site.

44. The apparatus of Claim 41, wherein said calibration is developed using multivariate analytical techniques, and wherein said model implicitly incorporates said shift information in multivariate regression coefficients.

45. The apparatus of Claim 44, wherein said tissue state parameter is monitored by:

calculating an absorbance spectrum from said NIR spectrum;

optionally, pre-processing said absorbance spectrum; and

calculating a skin temperature value by applying said multivariate calibration model.

46. The apparatus of Claim 44, wherein said tissue state parameter is modified by applying one or both of said means of control so that skin temperature is restored to said target range.

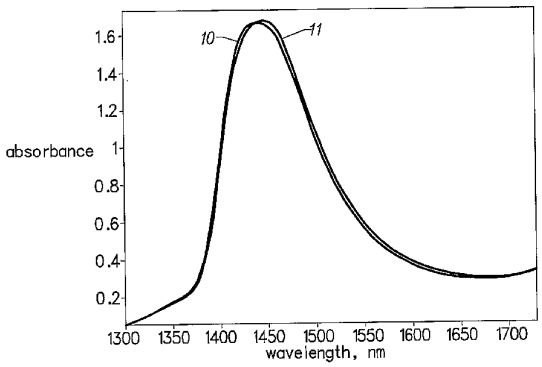
absorbance
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
10
11
1300
1350
1400
1450
1500
1550
1600
1650
1700
wavelength, nm

FIG. 1

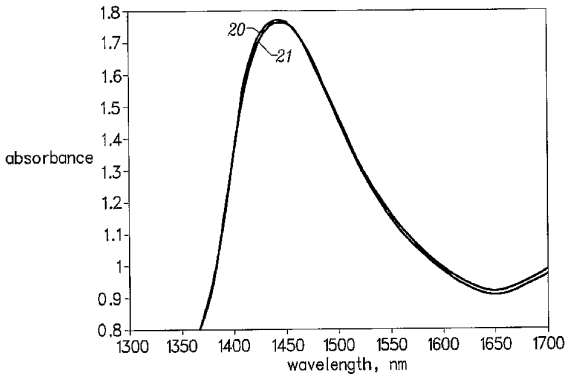
absorbance
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
20
21
1300 1350 1400 1450 1500 1550 1600 1650 1700
wavelength, nm

FIG. 2

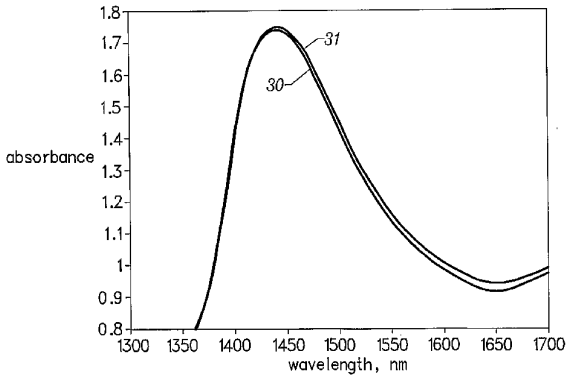
absorbance
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
31
30
1300 1350 1400 1450 1500 1550 1600 1650 1700
wavelength, nm

FIG. 3

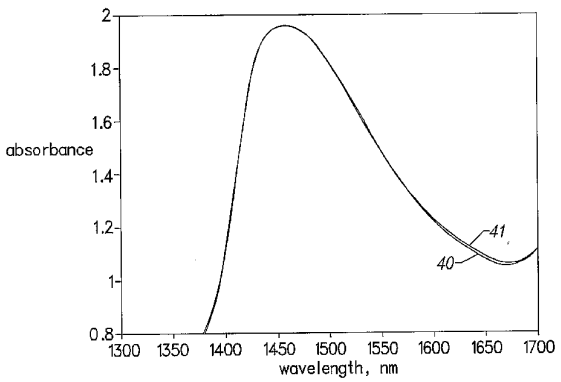
absorbance
2
1.8
1.6
1.4
1.2
1
0.8
1300 1350 1400 1450 1500 1550 1600 1650 1700
wavelength, nm
41
40

FIG. 4

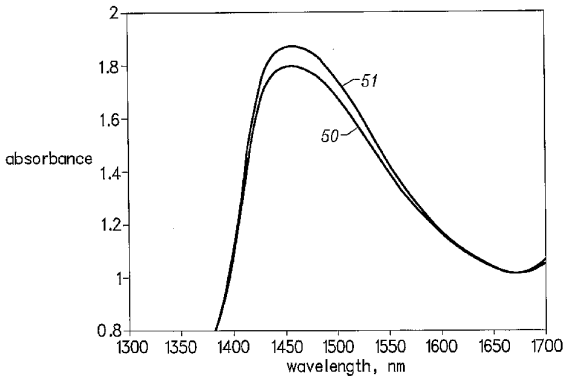
absorbance
2
1.8
1.6
1.4
1.2
1
0.8
1300 1350 1400 1450 1500 1550 1600 1650 1700
wavelength, nm
51
50

FIG. 5

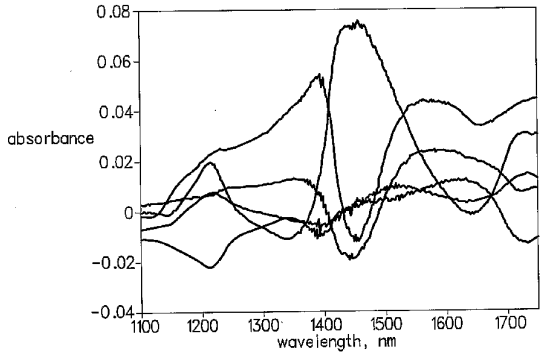
0.08
0.06
0.04
absorbance
0.02
0
-0.02
-0.04
1100 1200 1300 1400 1500 1600 1700
wavelength, nm

FIG. 6

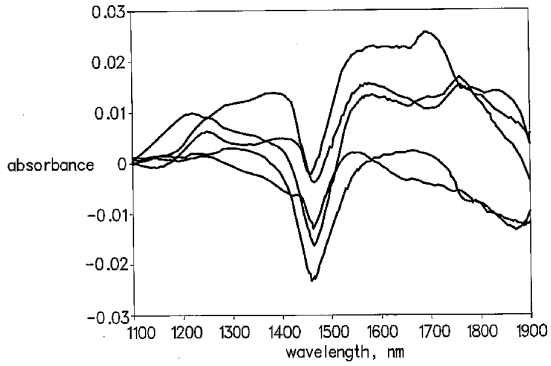
0.03
0.02
0.01
absorbance 0
-0.01
-0.02
-0.03
1100 1200 1300 1400 1500 1600 1700 1800 1900
wavelength, nm

FIG. 7

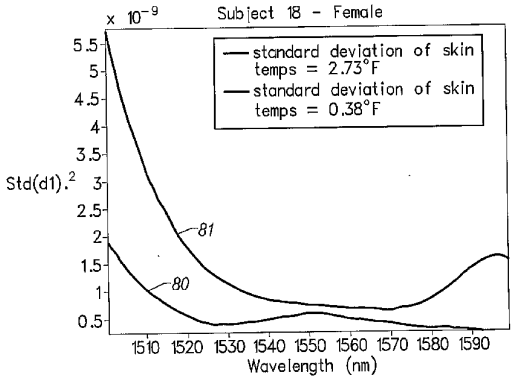
x 10⁻⁹
Subject 18 - Female
standard deviation of skin temps = 2.73°F
standard deviation of skin temps = 0.38°F
Std(d1).²
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
81
80
1510 1520 1530 1540 1550 1560 1570 1580 1590
Wavelength (nm)

FIG. 8

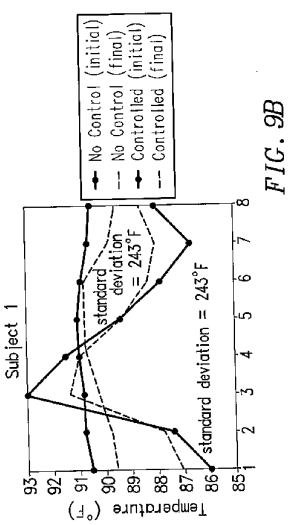

FIG. 9B

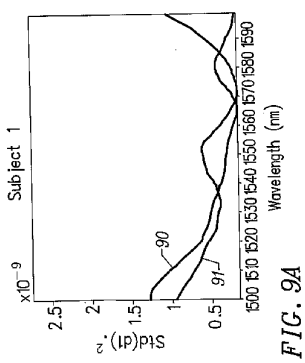

FIG. 9A

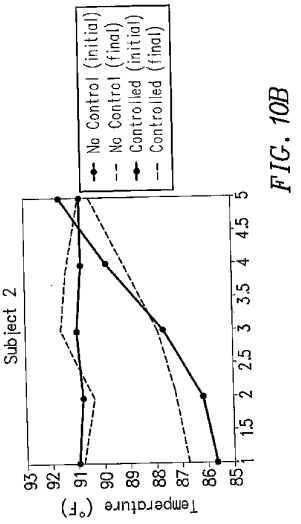

FIG. 10B

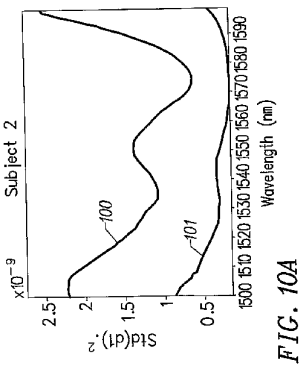

FIG. 10A

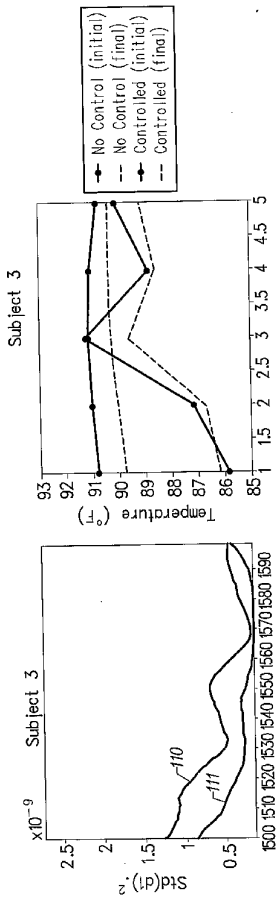

FIG. 11B

FIG. 11A

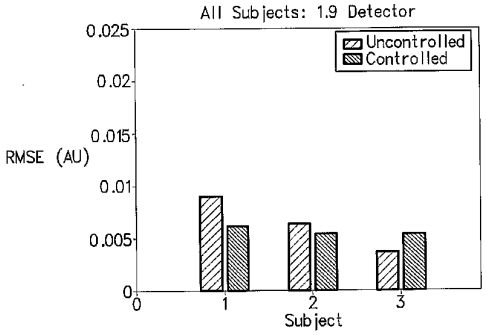
All Subjects: 1.9 Detector
Uncontrolled
Controlled
RMSE (AU)
0.025
0.02
0.015
0.01
0.005
0
0
1
2
3
Subject

FIG. 12


All Subjects: 2.6 Detector
Uncontrolled
Controlled
RMSE (AU)
0.025
0.02
0.015
0.01
0.005
0
0.5
1.5
2.5
3.5
Subject

FIG. 13

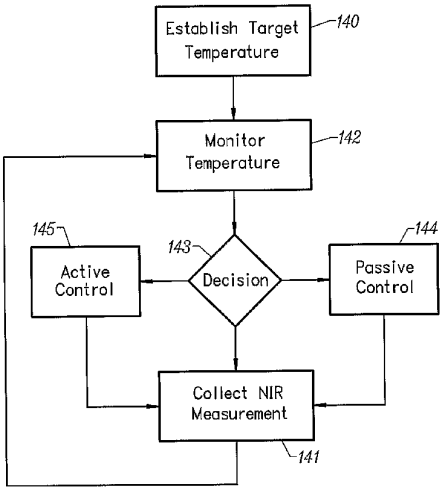
Establish Target Temperature
140
Monitor Temperature
142
145
143
144
Active Control
Decision
Passive Control
Collect NIR Measurement
141

FIG. 14

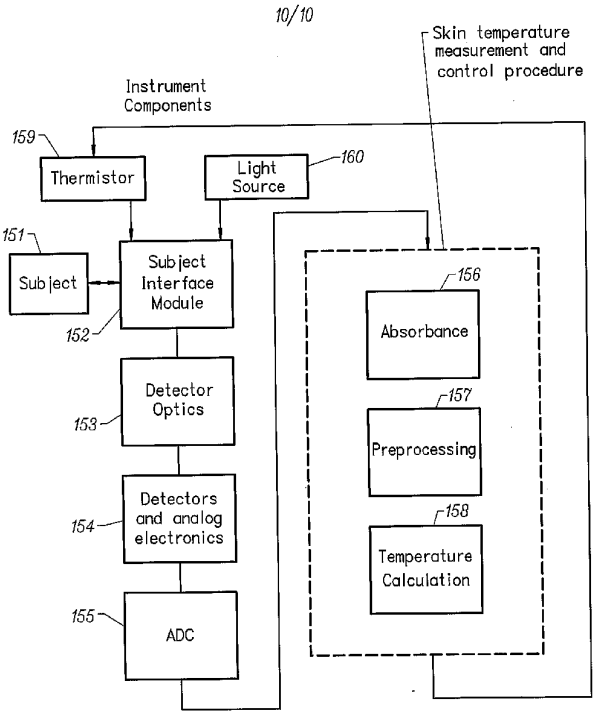
Skin temperature measurement and control procedure
Instrument Components
159
Thermistor
Light Source
160
151
Subject
Subject Interface Module
152
156
Absorbance
157
Preprocessing
158
Temperature Calculation
Detector Optics
153
Detectors and analog electronics
154
155
ADC

FIG. 15

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/29177

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61B 5/00
US CL : 600/549
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 600/309, 310, 316, 365, 473, 474, 475, 549

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST
search terms: blood, analyte, skin, temperature, infrared, target range, spectral, calibration, spectroscopic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, E	US 6,309,884 B1 (COOPER et al) 30 October 2001, see entire document.	1-46N
A, P	US 6,241,663 B1 (WU et al) 05 June 2001, see entire document.	1-46
A	US 6,072,180 A (KRAMER et al) 06 June 2000, see entire document.	1-46
A	US 6,025,597 A (STERLING et al) 15 February 2000, see entire document.	1-46

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 JANUARY 2002	11 MAR 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHARLES MARMOR, II Diane Smith Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet) (July 1998)*

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Ｆターム(参考) 2G059 AA06 BB12 BB13 DD16 EE01 EE12 GG10 HH01 JJ01 JJ11
JJ17 KK01 KK03 KK09 MM01 MM02 MM14 NN02
4C038 KK10 KL07 KM03 KX01 KY07

专利名称(译)	在基于NIR的血液样本确定期间最小化光谱效应		
公开(公告)号	JP2004510146A	公开(公告)日	2004-04-02
申请号	JP2002529955	申请日	2001-09-18
申请(专利权)人(译)	Forsythensis医疗墨		
[标]发明人	マカレウィックスマーシーアール マッツムツア ブランクトーマスビー モンフレステファンエル ルッチチモシーエル		
发明人	マカレウィックス マーシー アール マッツ ムツア ブランク トーマス ビー モンフレ ステファン エル ルッチ チモシー エル		
IPC分类号	G01N21/27 A61B5/00 A61B5/01 A61B5/145 A61B5/1455 A61B5/1495 G01N21/35		
CPC分类号	A61B5/1495 A61B5/14532 A61B5/1455 A61B5/1491		
FI分类号	G01N21/27.F A61B5/00.101.E G01N21/35.Z A61B5/14.310		
F-TERM分类号	2G059/AA06 2G059/BB12 2G059/BB13 2G059/DD16 2G059/EE01 2G059/EE12 2G059/GG10 2G059/HH01 2G059/JJ01 2G059/JJ11 2G059/JJ17 2G059/KK01 2G059/KK03 2G059/KK09 2G059/MM01 2G059/MM02 2G059/MM14 2G059/NN02 4C038/KK10 4C038/KL07 4C038/KM03 4C038/KX01 4C038/KY07		
优先权	60/235369 2000-09-26 US 09/955531 2001-09-17 US		
外部链接	Espacenet		

摘要(译)

要解决的问题：提供一种方法和装置，以最小化由于组织状况的变化而引起的非侵入性体内光谱测量中的混杂效应。 在目标范围内提供了一种用于最小化由组织状况的变化引起的无创体内光谱测量中的混杂效应的方法和设备，在该目标范围内，由于所选参数的变化而引起的光谱效应被最小化。 ，监视选定的组织状态参数。 本发明包括用于将选择的组织状况参数保持在目标范围内的主动和被动控制装置。

図 1 】

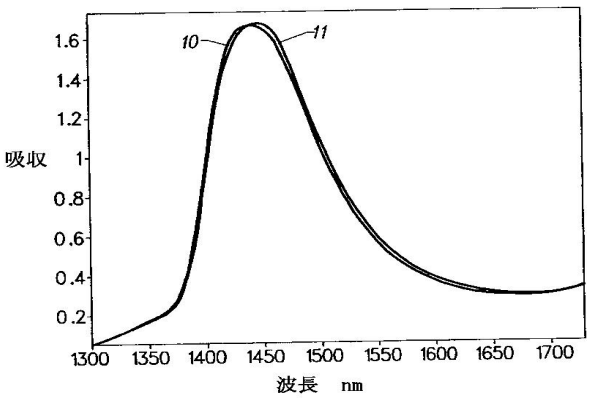

図 2 】