

(19) 日本国特許庁(JP)

## (12) 公表特許公報(A)

(11) 特許出願公表番号

特表2004-502957

(P2004-502957A)

(43) 公表日 平成16年1月29日(2004.1.29)

(51) Int.Cl.<sup>7</sup>

G01N 21/17

A61B 1/00

G02B 23/26

H04N 5/335

F 1

G01N 21/17

A61B 1/00

G02B 23/26

H04N 5/335

620

300D

B

V

テーマコード(参考)

2 G059

2 H040

4 C061

5 C024

審査請求 未請求 予備審査請求 有 (全 186 頁)

(21) 出願番号 特願2002-509751 (P2002-509751)  
 (86) (22) 出願日 平成13年7月10日 (2001.7.10)  
 (85) 翻訳文提出日 平成15年1月10日 (2003.1.10)  
 (86) 國際出願番号 PCT/CA2001/000992  
 (87) 國際公開番号 WO2002/004929  
 (87) 國際公開日 平成14年1月17日 (2002.1.17)  
 (31) 優先権主張番号 60/217,090  
 (32) 優先日 平成12年7月10日 (2000.7.10)  
 (33) 優先権主張国 米国(US)

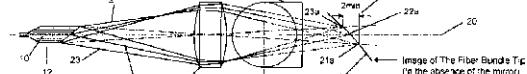
(71) 出願人 503020529  
 ユニヴァーシティー ヘルス ネットワー  
 ク  
 UNIVERSITY HEALTH N  
 ETWORK  
 カナダ国 エム2ジー 2エム9 オンタ  
 リオ州 トロント ユニヴァーシティー<sup>4</sup>  
 アヴェニュー 610 ルーム 7-50  
 (74) 代理人 100073184  
 弁理士 柳田 征史  
 (74) 代理人 100090468  
 弁理士 佐久間 剛

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(54) 【発明の名称】高分解能コヒーレント光画像化のための方法及び装置

## (57) 【要約】

試料の表面下微細構造を検査するための方法及び装置が提供される。複数の光放射源からの光が第1の光路に沿って進行する。第1の光路において、装置はそれぞれの光源からの光を第1の光路に沿う複数の焦点のそれぞれに集束させて、第1の光路の選ばれた部分の実質的に連続な覆域を提供する。次いで、試料内に延び込む選ばれた長さの範囲内にある第1の光路上の試料が、第1の光路の選ばれた範囲に沿って走査される。



**【特許請求の範囲】****【請求項 1】**

試料の光検のための装置において、前記装置が：  
複数の個別光放射源を提供するための光源手段；  
前記光源手段から延びる第1の光路；  
前記第1の光路の選択された範囲の実質的に連続な覆域を提供するために、前記光放射源からの光を前記第1の光路内の表面の上に位置する複数の焦点のそれぞれに集束させるための、前記第1の光路にある集束手段であって、使用においては、前記選択された範囲内の少なくとも一部に試料を配置することができ、よって前記試料内の複数の点の同時走査を可能にするものである集束手段；  
ことを特徴とする装置。

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**【請求項 2】**

前記光源手段が一次光源及び、前記一次光源を前記光放射源に結合し、複数本の光ファイバを含む、光結合手段を備えることを特徴とする請求項1に記載の装置。

**【請求項 3】**

前記複数本の光ファイバがファイバ束チップで終端し、前記ファイバ束チップ内の前記光ファイバの末端には前記第1の光路に沿って互いに對して段差が付けられ、前記複数本の光ファイバのそれぞれからの光が相異なる焦点に集束されることを特徴とする請求項2に記載の装置。

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**【請求項 4】**

前記第1の光路内に、前記表面の回転運動を可能にするために光放射源からの光を偏向させるための、可回転ミラーを備えることを特徴とする請求項1，2または3に記載の装置。

**【請求項 5】**

前記第1の光路内にミラーを備え、前記光源手段、前記集束手段及び前記ミラーを、結合して、前記表面の直線並進運動を可能にするために直線的に並進させ得ることを特徴とする請求項1，2または3に記載の装置。

**【請求項 6】**

前記第1の光路内に可回転ミラーを備え、前記光源手段、前記集束手段及び前記可回転ミラーを、結合して、前記表面のヘリカル運動を可能にするために直線的に並進させ得ることを特徴とする請求項1，2または3に記載の装置。

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**【請求項 7】**

前記表面が複雑な表面であることを特徴とする請求項4，5または6に記載の装置。

**【請求項 8】**

前記ミラーがプリズムの表面であることを特徴とする請求項4，5または6に記載の装置。

**【請求項 9】**

前記ミラーに結合された、前記ミラーを回転させるためのミクロ機械加工電気機械システムを備えることを特徴とする請求項4または6に記載の装置。

**【請求項 10】**

前記光源手段、前記集束手段及び前記ミラーを直線的に並進させるためのミクロ機械加工電気機械システムを備えることを特徴とする請求項5または6に記載の装置。

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**【請求項 11】**

前記一次光源と前記光ファイバとの間の複数の光結合器、前記光結合器に結合された光遅延発生器及び前記光結合器に結合された検出器手段をさらに備え；前記光結合器は、前記一次光源からの光の一部を前記第1の光路に沿って送り、また前記一次光源からの光の一部を前記光遅延発生器に送り；前記光遅延発生器は第2の光路を提供し；ここで前記第1及び第2の光路に沿って前記光結合器に戻る光の間に干渉効果が生じ；前記光結合器が前記第1及び第2の光路に沿って戻った光を前記検出器手段に送ることを特徴とする請求項2，3または4に記載の装置。

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**【請求項 1 2】**

複数の一次光源及び複数のツリー型結合器を備え、前記複数のツリー型結合器のそれぞれは、前記複数の一次光源内の1つと関係付けられ、前記1つの一次光源を前記光結合器の内の少なくとも1つに結合することを特徴とする請求項11に記載の装置。

**【請求項 1 3】**

回収光を前記検出器手段に与えるために前記光結合器と前記検出器手段との間に配置された、複数の光サーチュレータを備えることを特徴とする請求項12に記載の装置。

**【請求項 1 4】**

複数本の光ファイバが前記光結合器を前記光遅延発生器に結合し、前記光遅延発生器は回折格子及び走査ミラーを有し、前記走査ミラーは軸を有し；前記回折格子が前記複数本の光ファイバのそれからの光を前記走査ミラー上に直線的に配向されるスペクトル成分に分解し；前記スペクトル成分の中点が前記スペクトル成分を位相変調するために距離 $\times d$ だけ前記走査ミラーの前記軸からオフセットされていることを特徴とする請求項11に記載の装置。

**【請求項 1 5】**

前記複数の光結合器のそれを位相変調器に結合するための第1の複数本の光ファイバ及び前記位相変調器のそれを前記光遅延発生器に結合するための第2の複数本の光ファイバを備え、前記光遅延発生器は回折格子及び走査ミラーを有し、前記走査ミラーは軸を有し；それぞれの光ファイバについて、前記位相変調器が前記光を位相変調し、前記回折格子が前記位相変調された光を前記走査ミラー上に直線的に配向されるスペクトル成分に分解し、前記スペクトル成分の中点が前記走査ミラーの軸上に向けられ；それぞれの光ファイバからの前記スペクトル成分が別の光ファイバからの光の前記スペクトル成分と間隔をおいて配置されていることを特徴とする請求項11に記載の装置。

**【請求項 1 6】**

複数本の光ファイバを備え、前記複数本の光ファイバのそれは前記複数本の光ファイバのそれからの光を第1の光ファイバに結合するために前記複数の光結合器のそれをツリー型結合器に結合し、前記第1の光ファイバは前記結合された光を位相変調するための位相変調器に結合され；前記位相変調器を前記光遅延発生器に結合するための第2の光ファイバを備えることを特徴とする請求項11に記載の装置。

**【請求項 1 7】**

前記装置が、身体の内部検査のための内視鏡として構成され；前記第1の光路、前記集束手段及び前記ミラーが前記内視鏡内に備えられ；前記内視鏡が、少なくとも1つの白色光照明用チャネル、白色光内視鏡前面観察用チャネル、空気ノズル及び水ノズルの内の1つのためのチャネル、及び吸引／生検チャネルの内の少なくとも1つを備えることを特徴とする請求項4，5または6に記載の装置。

**【請求項 1 8】**

前記内視鏡が動径、並進またはヘリカル走査を行うように適合されていることを特徴とする請求項17に記載の装置。

**【請求項 1 9】**

前記内視鏡が駆動機構としてミクロ機械加工電気機械システムをさらに備えることを特徴とする請求項18に記載の装置。

**【請求項 2 0】**

試料の光検のためのNチャネル装置において、前記Nチャネル装置が複数の光ネットワーク及び基準アームを備え、前記複数の光ネットワークのそれが、前記Nチャネル装置のための1つのチャネルを提供し、前記基準アームを共有することを特徴とするNチャネル装置。

**【請求項 2 1】**

前記光ネットワークが、検出器、光結合手段及び試料アームを備え、前記光結合手段が、前の光ネットワークから光を受け取り、次の光ネットワークに光を送るように構成されていることを特徴とする請求項20に記載のNチャネル装置。

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**【請求項 2 2】**

前記試料アームが偏光制御手段、可変遅延素子及び試料を備えることを特徴とする請求項21に記載のNチャネル装置。

**【請求項 2 3】**

前記基準アームがツリー型結合手段、位相変調手段及び光遅延手段を備えることを特徴とする請求項20に記載のNチャネル装置。

**【請求項 2 4】**

試料の光検のための2チャネル装置において、前記2チャネル装置が、請求項20, 21, 22, 23に記載の光ネットワークを2つ備え、さらに光源及び前記2チャネル装置の方向を案内するための可視光源を備えることを特徴とする2チャネル装置。 10

**【請求項 2 5】**

試料の光検のための方法において、前記方法が：

- (a) 複数の個別光放射源から、第1の光路に沿う、光を提供するステップ；
  - (b) 前記第1の光路内に集束手段を提供するステップ；
  - (c) 前記第1の光路の選択された範囲の実質的に連続な覆域を提供するために、前記第1の光路内の表面に沿う複数の焦点のそれぞれに前記光放射源からの前記光を集束させるステップ；
  - (d) 前記第1の光路内に少なくとも一部が位置する試料を提供するステップ；及び
  - (e) 前記試料内の複数の点を同時に走査するステップ；
- を含むことを特徴とする方法。 20

**【請求項 2 6】**

一次光源から光を提供するステップ及び前記光を複数本の光ファイバを介して前記複数の個別光放射源に送るステップを含むことを特徴とする請求項25に記載の方法。

**【請求項 2 7】**

前記複数本の光ファイバをファイバ束チップに終端させるステップ、前記光ファイバの末端を共通平面内で前記ファイバ束チップに設けるステップ、前記第1の光路に沿って前記光ファイバの末端に互いに段差を付けるステップ、及び前記光ファイバからの光を共通レンズにより集束させるステップを含むことを特徴とする請求項26に記載の方法。 30

**【請求項 2 8】**

請求項27に記載の方法において：

- (a) 前記第1の光路内に可回転ミラーを提供するステップ；
  - (b) 前記第1の光路を偏向させるステップ；
  - (c) 前記複数の焦点を一表面上に配置するステップ；
  - (d) 軸方向走査を実施するステップ；
  - (e) 前記表面を移動させるために前記ミラーを回転させるステップ；及び
  - (f) 前記ステップ(d)を少なくとも2回反復し、それぞれの反復の間に前記ステップ(e)を実施するステップ；
- を含むことを特徴とする方法。 40

**【請求項 2 9】**

請求項27に記載の方法において：

- (a) 前記第1の光路内にミラーを提供するステップ；
  - (b) 前記第1の光路を偏向させるステップ；
  - (c) 前記複数の焦点を一表面上に配置するステップ；
  - (d) 軸方向走査を実施するステップ；
  - (e) 前記表面を移動させるために、前記集束手段、前記複数の光放射源及び前記ミラーを、結合して、直線的に並進させるステップ；及び
  - (f) 前記ステップ(d)を少なくとも2回反復し、それぞれの反復の間に前記ステップ(e)を実施するステップ；
- を含むことを特徴とする方法。 50

**【請求項 3 0】**

請求項 27 に記載の方法において：

- (a) 前記第1の光路内にミラーを提供するステップ；
  - (b) 前記第1の光路を偏向させるステップ；
  - (c) 前記複数の焦点を一表面に配置するステップ；
  - (d) 軸方向走査を実施するステップ；
  - (e) 前記表面を移動させるために、前記ミラーを回転させると同時に、前記集束手段、前記複数の光放射源及び前記ミラーを、結合して、直線的に並進させるステップ；及び
  - (f) 前記ステップ (d) を少なくとも2回反復し、それぞれの反復の間に前記ステップ (e) を実施するステップ；
- を含むことを特徴とする方法。

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【請求項 31】

前記ミラーとしてプリズムの表面を提供するステップを含むことを特徴とする請求項 28, 29 または 30 に記載の方法。

【請求項 32】

複数の結合器を介して前記一次光源から前記複数本の光ファイバに光を供給するステップ；前記光結合器に接続された光遅延発生器を提供し、第2の光路を提供するステップ；干渉パターンを形成するため、前記第1及び第2の光路に沿う前記結合器への光の送り戻しを可能にするステップ；及び、前記干渉パターンの検出のため、前記光結合器において前記第1及び第2の光路から受け取った光を検出手段に送るステップを含むことを特徴とする請求項 28, 29 または 30 に記載の方法。

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【請求項 33】

複数の一次光源を提供し、前記複数の一次光源のそれぞれに対して、それぞれのツリー型結合器を提供するステップ；及び前記複数の一次光源のそれぞれを前記それぞれのツリー型結合器を介して前記光結合器のそれぞれに結合するステップを含むことを特徴とする請求項 32 に記載の方法。

【請求項 34】

回収光を前記検出手段に与えるために、前記光結合器と前記検出手段との間に光サーチュレータ手段を提供するステップを含むことを特徴とする請求項 32 に記載の方法。

【請求項 35】

請求項 1 から 24 のいずれかに記載の装置を、少なくとも1つの白色光照明用チャネル、白色光内視鏡前面観察チャネル、吸引／生検チャネル並びに空気ノズル及び水ノズルの内の1つのためのチャネル、の内の少なくとも1つを備える、身体の内腔の検査のために適合された内視鏡として提供するステップを含むことを特徴とする請求項 33 に記載の方法。

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【請求項 36】

前記光放射源を含む媒体と前記試料との間の屈折率の変化があり、それぞれの焦点に対して、前記試料内の実際の前記光放射源のそれぞれのコヒーレンスゲートと前記焦点の位置との間の前記屈折率変化による変位間隔が：

- (a) 前記光放射源の前記焦点が前記光放射源を含む前記媒体から前記試料内に延びる光路に沿って配列されるように、前記第1の光路において前記複数の光放射源からの光を走査するステップ；

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- (b) 前記焦点のそれぞれについて反射光を検出するステップ；及び

- (c) 隣接する焦点に比較して反射光に大きな変化がある焦点の位置を突き止めるステップ；

にしたがい、前記ステップ (c) で位置が突き止められた前記焦点が前記試料と前記光放射源を含む前記媒体との間の界面の位置を示すことにより；

得られることを特徴とする請求項 30, 31 または 32 に記載の方法。

【請求項 37】

前記方法が、選択された走査域に対して適切な空間分解能を得るために、それぞれの軸方向走査について前記ステップ (a) から (c) を繰り返すステップをさらに含むことを特

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徵とする請求項 3 6 に記載の方法。

【発明の詳細な説明】

【0001】

発明の分野

本発明は高分解能光画像化のための方法及び装置のいずれにも関する。さらに詳しくは、本発明は内視鏡への組込に適する高分解能画像化の提供に関する。

【0002】

発明の背景

現代の医用画像化手法は、健康管理への応用に重要になっている。X線コンピュータ連動断層撮影(CT)、磁気共鳴画像法(MRI)及び超音波画像法のような手法は、現代の医療センターのほとんどで利用できる主要な断層撮影法である。可視光内視鏡検査法は、気管支鏡検査または結腸鏡検査のような処置に広く用いられる別の主要な画像化手法である。これらの手法のそれぞれは、様々な物理的原理を採用し、検査下の生物学的組織の様々な特性を様々な分解能で測定する。さらに、これらの手法は生体内で普通に実施できる。第3のタイプの画像化手法である光学顕微鏡検査法も、未だに診療医学において広く利用されている。しかし、現時点では光学顕微鏡検査法は切除または摘出試料の詳細な検査に限られ、生体内では用いられていない。多くの情況において、光学顕微鏡検査法によって与えられる優れたコントラスト及び分解能は、生体組織摘出及びこれに続く光学顕微鏡による組織検査が診断に対する黄金律的標準と見なされるほどである。

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【0003】

低分解能断層撮像手法を、高分解能画像化、生体組織検査法または介入処置とともに使用するような、上記の手法の併合が絶えず研究され、評価されている。そのような手法の評価は、技術上の実行可能性、臨床上の恩恵及び費用に基づいている。

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【0004】

光コヒーレンス断層撮影法(OCT)は、生物学的組織のような混濁した高散乱性の媒質において高分解能深度プロファイル測定を可能にする、電磁放射の低コヒーレンス特性に基づく比較的新しい画像化手法である。生物医学的画像化におけるOCTの利用は、現在いくつかの公立及び私企業の研究所で研究されている。OCTの主要な利点は、組織の表面下部位からの反射深度を局限化できるという能力にある。この局限化は用いられる光源のコヒーレンス特性により本質的に決定され、選択された近赤外線(IR)源(例えば、レーザまたは增幅自然放出発光装置)に対して2から20μmもの狭い範囲とすることができます。このことから、OCTで達成し得る深度分解能の尺度が与えられる。コヒーレンス性とは無関係に、横方向分解能は画像化深度におけるビーム断面積及び取得データの横方向間隔により決定される。文献における横方向間隔の一般値は5から30μmの範囲にある。この混濁組織を損なわない優れた断層画像化能力に対して払われなければならない代償は、多重散乱及び吸収により光のコヒーレンス及び侵入深度がともに低下して、OCT画像化深度がほぼ2ないし3mmになるので、画像化深度が制限されることである。

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【0005】

現在のOCTの実施態様のほとんどは、入射コヒーレント光ビームをミラーをもつ基準光路(すなわち基準アーム)及び被検試料をもつ試料光路(すなわち試料アーム)に導く50/50ビームスプリッタによる、マイケルソン干渉法に基づく。この方式の自由空間光学系及びファイバ光学系実施態様のいずれもが現在用いられている。基準アームのミラーからの反射ビーム及び試料アームの組織からの反射ビームが同じスプリッタで結合され、生じる光エネルギーの1/2が検出器に当たる。2本のビームの光路長が光源のコヒーレンス長の範囲内で一致する場合を除いては、一般に2本の光束の非コヒーレントな重畳がおこる。この限界距離内では、2本の光束のコヒーレントな重畳により、特定の深度における組織の反射率に比例する強さの干渉縞をもつ干渉パターンが得られる。次いで、試料の深度プロファイル測定が、基準アーム長を走査することにより、さらに正確には、基準アームにおいて時間遅延を用いて(これは基準アームを長くすることと等価である)基準アームの光路長を走査することにより、達成される。大きな背景拡散反射に埋もれてい

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る上記のかすかな振幅変調を測定して定量するために、ダイナミックレンジがほぼ70から110dBの、様々な検出方法が開発されている。さらに、ビームの横方向並進及び基準ミラーの軸方向移動により、所望の視野にわたる2次元反射率画像を構成することが可能になる。デコンボリューションによる画像処理の実施のような、最終画像の品質を向上させる手段も研究されてきた。

#### 【0006】

上述は通常の反射率OCT画像化の簡単な説明である。その他の変形には、例えば、フロー(ドップラー)画像化及び(OCT光学系及び/または信号処理手法がさらに複雑化するという犠牲は払うものの)偏光画像化がある。これらの別の手法による画像は普通、通常のOCTによる画像とともに得られ、よっていくつかの画像の重ね合わせまたは融合が可能である。技術開発及び/または臨床への実施がさらに進めば、医学におけるOCTの臨床上の有用性を高めるに十分な情報内容を付け加えることができる。10

#### 【0007】

しかし、研究開発され実験室ではうまくはたらいたOCTシステムの構成及び手法の多くは、そのままでは胃腸または気管支の内視鏡検査のような生体内画像化に適していない。むしろ、そのようなOCTシステムは、皮膚科、眼科及び歯科での応用により適するといえる。対照的に、生体内OCT画像化は、速度、分解能、コントラスト、侵入深度及び機器寸法の課題に取り組まなければならない。画像は患者の動きの影響を無視できるに十分に迅速に得られなければならず、それでも適切な軸方向及び横方向分解能が得られ、内視鏡として有用であるに十分に小さい機器寸法が維持されなければならない。生体内内視鏡検査に課せられた困難な課題を克服するための、強力な近IR源、基準アーム長を高速で変化させる手段及び特注の遠端光学装置の開発が行われ、成功している。20

#### 【0008】

最新のOCT技術は、単一モード光ファイバを従来の白色光内視鏡のアクセサリーチャネルに組み入れられた遠端断層観察光学系とともに採用している。画像を構成するため、OCTファイバの観察方向がほぼ2mmの距離にわたり前後に直線的に走査され、また柔軟なガイドワイヤまたはインターロック付歯車機構によって毎秒数回転で回転される。この並進または回転と同時に、深度方向走査(すなわちA-走査)をおこさせるために内視鏡の外にある基準アームの長さが光位相遅延により迅速に変えられる。現在、これらのOCTシステムは通常のビデオレートまでのフレームレートで動作するが、より一般的には毎秒4から8フレームで動作し、1フレームは2から3mmの深度までの十分な周辺観察像を提供する。得られる分解能値は、深度(軸)方向でほぼ5から25μmであり、横方向ではほぼ20から40μmである。さらに、横方向分解能は一般に、等比発散により、OCT装置のファイバチップからの距離が大きくなるにつれて低下する。これらのOCTシステムは、雑音レベルが高く、画像化速度が速いために、ダイナミックレンジが生体外システムに対応するダイナミックレンジより若干低い。30

#### 【0009】

最新のOCT技術に基づくと、コヒーレント生体内OCTシステムが臨床画像化に成功するに十分であるかは疑問である。画像は確かに有用であるが、“光生検”という逃げ水のような目標が実現されるべきであるならば、かなりの改善が必要である。例えば、軸方向及び横方向の分解能は改善できる。軸方向分解能の改善には通常、より良好な低コヒーレンス光源(すなわちCW(連続波)及びパルス光源)の使用が含まれるが、最適に近い、深度可変の、横方向分解能の問題は処理が一層困難である。体外システムでは、速度及び物理的寸法の制限が緩和され、横方向解像度は高NA(開口数)対物レンズを用いてビームを数μmまで集束させることにより改善される。従来のOCT走査とは対照的に、この場合には、光路長差の振動を小さくしてあらかじめ選択された深さで横(面内)方向に画像化を行い、続いて深度を必要なだけ少量増分して次の画像化を行うことができる。高NA対物レンズは屈折率整合液を介して組織に結合されることが多い。OCTを高NA遠端光学レンズとともに用いる手法は総じて光コヒーレンス顕微鏡法(OCTM)として知られる。しかし、ビームウエスト位置における改善された横方向解像度は、強集束ビームの焦4050

点深度が非常に浅いため、他の深度においては横方向ぼけという犠牲を払うことになる。したがって、様々な深度に集束させるためにレンズ - 表面間隔を変えなければならない。さらに、動的トラッキング方式では、コヒーレンスゲート（コヒーレンスゲート内では試料アームからの光ビームと基準アームからの光ビームとの間でコヒーレント干渉が可能である）の位置とビームウェストの位置が同じ深度に保たれる必要がある。横方向分解能改善のための上記の手法は、寸法及び速度要件のため、生体内内視鏡については試みられてこなかった。

#### 【0010】

##### 発明の概要

本発明は、以降内視顕微鏡と称することとする、顕微的分解能をもつ内視鏡光コヒーレンス断層撮影（OCT）装置を提供するという概念に基づく。内視顕微鏡の考え得る臨床上の応用の考察の結果、以下のパラメータ及び特徴が、現在の生体内OCTシステムと同時にこれらのパラメータ及び特徴を達成することは困難であることから、弁別された。

#### 【0011】

##### 1. 高分解能

細胞レベル及び細胞より小さいレベルの分解能を達成するためには、内視顕微鏡は、好ましくは軸方向及び横方向のいずれにおいても  $5 \mu\text{m}$  より小さい構造を解像すべきである。既存の生体内OCTシステムのほとんどとは対照的に、等比発散による、画像化されている組織の深度にともなう横方向分解能の実質的な低下が生じてはならない。

#### 【0012】

##### 2. 大視野

内視顕微鏡の適切な視野は、光軸の軸方向及び横方向においてほぼ  $2 \text{mm} \times 2 \text{mm}$  である。この視野で臨床上の応用には十分であると考えられる。画像全体にわたり軸方向及び横方向のいずれにおいても  $5 \mu\text{m}$  分解能を達成するためには、それぞれのフレームに対して 800 回をこえる A - 走査（すなわち深度走査）が行われなければならない。得られる画像は、640,000 をこえる画素をもつであろう。この画素数は既存の生体内OCTシステムより数桁大きい。

#### 【0013】

##### 3. 小寸法内視鏡チップ

既存の生体内OCTシステムのほとんどは、既存の内視鏡の計装チャネルの制約に基づいて設計されている。この結果、そのようなシステムの外径はほぼ 2 から 3 mm に抑えられ、このため撮像システムの開口数が制約される。このことから、生体内条件下で高い横方向分解能を得ることが困難になる。このような制約は技術上不要であり得るし、考察している臨床上の応用における OCT / OCM の恩恵の十全な活用を制限し得る。したがって、例えば 3 mm ないしそれ以上のようないくつかの外径を、20 mm より短い硬質チップ長とともに、内視鏡に用いることができる。

#### 【0014】

##### 4. 高画像化速度

内視顕微鏡は生体内条件下で高分解能の大面積画像化に用いられるであろうから、生理学的運動による組織の運動があるので、運動アーティファクトが考慮されなければならない。これらの運動アーティファクトは良好な画像品質を保証するために除去されるべきである。したがって、内視顕微鏡は、典型的な生理学的運動速度が 5 mm / 秒であるとすれば、画像 1 フレームを好ましくは 12.6 ミリ秒以内に取得できるべきである。これは、毎秒 63,000 回の A - 走査に相当する。この画像化速度は現在の生体内OCTシステムに比べて 1 枠より大きい。

#### 【0015】

##### 5. 現在利用可能な内視鏡画像化法との統合

臨床上の有用性を向上させるため、好ましくは従来の白色光画像化が内視顕微鏡に統合されるべきである。さらに、好ましくは、内視顕微鏡の誘導の下に切除生検が行われ得るように、計装チャネルが設計されるべきである。おそらくは、水及び空気の送配のための計

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装チャネルも利用可能にされることも好ましい。

【0016】

上に略述した内視顕微鏡のための高等な要件は既存のOCT/OCM設計とは相容れない。例えば、内視顕微鏡に6mmの外径が許容され、G.J.ティアニー(Tearney), M.E.ブレジンスキイ(Brezniski), B.E.ボウマ(Bouma), S.A.ボッパート(Boppert), C.ピトリス(Pitris), J.F.サザーン(Southern), 及びJ.G.フジモト(Fujimoto)('光コヒーレンス断層撮影法による生体内内視鏡光生検', Science, 1997年6月27日, 第276巻, p. 2037~2039)により説明されるような単一回転ファイバに基づく、遠端光学系構造が用いられれば、5μmの横方向分解能が走査のどの1つにおいても組織内の1つの特定の深度で達成され得るが、そのような横方向分解能は他の深度ではビーム発散により低下するであろう。さらに、所要の小寸法ビームウエストをつくるには高NAシステムが必要となるであろうから、L.M.シュミット(Schmitt), S.L.リー(Lee), 及びK.M.ユン(Yung)('厚い組織における分解能が高められた光コヒーレンス顕微鏡', Optics Communications, 1997年, 第142巻, p. 203~207)により説明されるようある種の動的補償を実施しなければ、かなりの(例: 2mm)距離にわたる深度においてコヒーレンスゲートと焦点とが一緒にとどまることはないであろう。したがって、上述した内視顕微鏡の要件の内のいくつかを達成するためには、(プローブ/組織間隔を変化させる)動的集束及び(光路長差を変化させる)動的補償が用いられなければならない。しかしこれらの集束及び補償手法では、実用装置の実現が面倒になり、高画像化速度要件を満たすことが一層困難になり得る。画像化速度を初めに満たすことを試みると、A.M.ローリンズ(Rollins), M.D.クルカーニ(Kulkarni), S.ヤズダンファー(Yazdanfar), R.ウング-アルニヤウジー(Ung-aranyawee), 及びJ.A.イザット(Izatt)('生体内ビデオレート光コヒーレンス断層撮影法', Optics Express, 1998年9月14日, 第3巻, 第6号, p. 219~229)によって説明されるように、画像分解能、特に横方向分解能が、装置の臨床上の有用性が損なわれる程度まで低下する。

【0017】

本発明は、既存の生体内または生体外OCT/OCMシステムに現在実施されているようなシリアル走査の代わりに、複数本のファイバ(すなわちチャネル)を採用して画像の様々な部分のパラレル走査を可能にするOCTを有する内視顕微鏡を提供する。それぞれのチャネルが非常に狭い軸方向範囲にかけてだけ高分解能OCTデータを収集する、組織内の様々な深度に集束される多パラレルチャネルを使用すれば、動的集束または動的補償を用いずに、視野全体にわたる密配置焦点列を得ることができる。これにより装置の構造が大いに簡素化され、この場合には、使用される光コンポーネントのほとんどを固定型とすることができる、高速動作を容易化することができる。さらに、ファイバ光学ベースのOCT手法では寸法が本質的に小さいから、多チャネル概念を屈曲性内視鏡装置で実施することが可能になり、一方で、患者の外部にある内視鏡の近端部には、光源、検出器及びその他の装備のための余裕ができる。

【0018】

本発明の第1の態様にしたがえば試料の光検のための装置があり、本装置は：

複数の個別光放射源を提供するための光源手段；

光源手段から延びる第1の光路；及び

第1の光路の選択された範囲の実質的に連続な覆域を提供するために光放射源からの光を第1の光路内の面上に位置する複数の焦点のそれぞれに集束させ、使用時には、試料の少なくとも一部を前記選択された範囲内に配置することができ、よって試料内の複数の点を同時に走査することを可能にするための、第1の光路内の集束手段；

を備える。

【0019】

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本発明の第2の態様にしたがえば試料の光検のためのNチャネル装置があり、本Nチャネル装置は複数の光ネットワーク及び1つの基準アームを備え、光ネットワークのそれぞれはNチャネル装置のための1チャネルを提供し、基準アームを共有する。

#### 【0020】

本発明の第3の態様にしたがえば試料の光検のための方法が提供され、本方法は：

- (a) 第1の光路に沿う、複数の個別光放射源からの光を提供するステップ；
- (b) 第1の光路内に集束手段を提供するステップ；
- (c) 第1の光路の選択された範囲の実質的に連続な覆域を提供するために、光放射源からの光を第1の光路内の面に沿う複数の焦点のそれぞれに集束させるステップ；
- (d) 第1の光路内に少なくとも一部が配置された試料を提供するステップ；

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及び

- (e) 試料内の複数の点を同時に走査するステップ；
- を含む。

#### 【0021】

本発明とともに使用するための試料がいかなる生物学的組織も、あるいはその他の適当な材料も含み得ることは当然である。

#### 【0022】

本発明のさらなる目的及び利点は、添付図面とともにになされる、以下の説明から明らかになるであろう。

#### 【0023】

##### 発明の詳細な説明

本発明の一層の理解のため及び本発明がどのようにしてに実行され得るかを示すため、例として、本発明の好ましい実施形態を示す図面がここで参照される。

#### 【0024】

以下の説明においては、撮像源により用いられる波長及び装置に用いられる光コンポーネントの物理的寸法のような、様々な特定の寸法及びその他のパラメータが記述される。これらの寸法及びパラメータは説明のためでしかなく、本発明を制限するものでないことは当然である。特定のパラメータ、寸法等は目的とする本発明の応用に依存して選択することができる。

#### 【0025】

図1を参照すれば、本発明は、多束単一モードファイバ10，ファイバ束チップ12，集束レンズ14及びミラー16を有する内視鏡コヒーレント光顕微鏡を備える装置を提供する。多束単一モードファイバ10及び集束レンズ14は静止しており、一方ミラー16は回転可能である。したがって、ミラー16は回転のために既知の態様で取り付けられている。ミラー16のための回転機構の詳細はこれ以上説明されないが、従来の機構とすることができる。（ほぼ50本のファイバとすることができる）多束単一モードファイバ10は、ファイバ束チップ12においてアレイを形成する。このアレイは開豁されて、図2に示されるように、“階段”パターンに配列される。ファイバ束チップ12から放射される光は集束レンズ14で集束され、ミラー16で反射される。集束レンズ14は、直径を5mm（すなわち $= 5\text{ mm}$ ）とし、焦点距離を5mm（すなわち $f = 5\text{ mm}$ ）とすることができます。ミラー16は、5mmの直径及び45°で開豁された前面を有することができます。ファイバ束チップ12の焦点の拡大像が図3に示される。

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#### 【0026】

図1aは、多束単一モードファイバ10から例として任意に選ばれた3本のファイバからの3本のビーム21，22及び23を示す。多束単一モードファイバ10が順次にずらされている、すなわち階段配列になっているという性質により（図2参照）、ビーム21，22及び23のそれぞれが相異なる点から発し、したがってミラー16が用いられていないときには、表面18上の相異なる点21a，22a及び23aに集束レンズ14により集束される。ファイバ束チップ12の多束単一モードファイバ10の全てが表面18上の相異なる点に集束されるビームを生じるという、同じ効果が得られることは理解されよう

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。参照数字 2 4 で示されるように（また図 3 に示されるように）、多束単一モードファイバ 1 0 が 5 0 本の光ファイバからなっており、それぞれのファイバからの光がほぼ 4 0  $\mu$ m の狭い範囲内に集束され、焦点が（集束レンズ 1 4 の軸 2 0 に沿って測定して）4 0  $\mu$ m ずつ間隔をおくように、それぞれのファイバの末端がずらして配置されていれば、合わせて 2 mm の範囲すなわち深度がカバーされる。集束レンズ 1 4 の軸 2 0 は第 1 の光路の一部である。

#### 【 0 0 2 7 】

ミラー 1 6 が存在すると、光ビーム 2 1 , 2 2 及び 2 3 は図 1 b 及び 1 c に示されるように集束される。すなわち、3 つの焦点 2 1 b , 2 2 b 及び 2 3 b は第 1 の光路の外延を形成する軸 2 6 に沿って垂直方向すなわち深度方向に間隔をおいて配される。図 1 c の端面図が示すように、3 つの焦点 2 1 b , 2 2 b 及び 2 3 b は、ミラー 1 6 の運動に対して円周方向にも間隔をおいて配される（すなわち、3 つの焦点は横方向に間隔をおいて配される）。3 つの焦点 2 1 b , 2 2 b 及び 2 3 b は表面 2 7 上に落ちて、第 1 の光路の選択された範囲の画像化を容易にする。表面 2 7 は複雑な表面であっても、平坦な表面であってもよい。多束単一モードファイバ 1 0 が 5 0 本の個別ファイバからなっていれば、ファイバ束チップ 1 2 からの全ての個別ファイバの焦点は、相応した間隔をおいて配されることになる。あるいは、反射された焦点 2 1 b , 2 2 b 及び 2 3 b は必ずしも軸 2 0 に垂直である必要はなく、軸 2 0 に対して大角をなしていればよい。

#### 【 0 0 2 8 】

ミラー 1 6 の回転の結果、表面 2 7 は移動する。これにより、図 1 c に示されるように、好みしい 2 mm × 2 mm の大きさの正方形の走査領域 2 8 をカバーする、2 次元 B - 走査画像 3 0 を得ることが可能になる。この B - 走査画像 3 0 は走査領域 2 8 に対して得ることができる画像の例を示す。

#### 【 0 0 2 9 】

例えば多束単一モードファイバ 1 0 のコア及びクラッド層の直径を変えることにより、多束単一モードファイバ 1 0 の構造を変えれば、表面 2 7 が変化する。さらに、多束単一モードファイバ 1 0 の代わりに光導波路ウエハを用いることもできる。

#### 【 0 0 3 0 】

代替実施形態において、図 1 d に示されるように、集束レンズ 1 4 及びファイバ束チップ 1 2 と結合して直線的に移動するミラー 1 6' でミラー 1 6 を置き換えることができる。直線並進には逆進運動を組み入れ得ることが好みしい。力学用語を用いれば、図 1 a に描かれるファイバ束チップ 1 2 は動径走査運動を利用する。動径走査運動は、食道または大腸のような、寸法がより大きい器官の走査に適切である。しかし、動径走査に必要な駆動機構は複雑であるため、ファイバ束チップ 1 2 の直径が大きくなり、血管のような内径の小さい器官の内視顕微鏡観察はできないであろう。したがって、動径走査の代わりに直線並進走査を行うように適合された、同様のファイバ束チップ 1 2' を備える、図 1 d に示される代替実施形態が用いられることになる。

#### 【 0 0 3 1 】

図 1 d に示されるように、上記の 2 つの走査方法の間の主要な違いは、ミラー 1 6' が回転せず、ファイバ束チップ 1 2' の全体が水平軸に沿って、例えば 4 mm の範囲にわたり、好みしくは可逆運動で並進されなければならないことである。機械的には、直線並進走査運動は動径走査運動ほど複雑ではない。さらに、直線並進走査は血管のような内径の小さい器官内の内視顕微鏡観察により一層適する。しかし、大腸のような、より大きいくつかの器官に対しては、直線並進走査は位置決めが困難なためそれほど適切ではない。

#### 【 0 0 3 2 】

別の代替実施形態において、上記の走査運動の両者を組み合せてヘリカル走査を行う内視顕微鏡観察装置を作成することができる。ヘリカル走査運動は、ミラー 1 6 , 集束レンズ 1 4 及びファイバ束チップ 1 6 の直線並進と組み合された、ミラー 1 6 の回転運動を含むことになる。そのような内視顕微鏡観察装置は、ヒトの大腸のような、ある種の器官の画像化により一層適し得る。ヘリカル走査内視顕微鏡観察装置は、図 1 a に示される装置

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を直線並進させることにより実施できる。

【0033】

また別の代替実施形態において、ファイバ束チップ12をミクロ機械加工電気機械システム（MEMS）駆動機構を用いるように変更することができる。上述した実施形態ではミラー16の何らかの形態の運動が必要であるから、機械的駆動機構が全実施形態で必要となる。したがって、内視鏡外部にモーターが配備され、機械的連結駆動機構またはワイヤが内視鏡の全長に沿って配置される。しかし、多チャネルファイバ光学構造は、そのような機械的駆動手段に束縛されない。実際、多チャネルシステムで実現可能な空間分解能は極めて高いため、機械的駆動手段が用いられる場合には、振動誘起偏光依存性のような、機械的駆動手段からの悪影響が本発明の十全な潜在能力を制限しかねない。したがって、電気的駆動型マイクロマシン光学装置を用いて走査を容易にする、MEMS電気的駆動機構を採用することができる。MEMS実施態様はミラー16のような並進させられる物体の近傍を除いて装置軸に沿う振動を低減するから、本実施態様は、機械的駆動機構により生じ得る悪影響をおそらくは回避し得る。MEMS実施態様は、小形化及び性能に関する利点も提供し得る。10

【0034】

別の代替実施形態においては、ファイバ束チップがミラー16を必要としないようにすることができる。ファイバ束チップ12及び集束レンズ14の結合体を軸回転可能のように取り付けることができる。そうすれば、軸回転運動により、試料内に広がる複数の面の各部分に沿って複数の焦点を導き、走査領域28のB-走査画像30を構成するように、ファイバ束チップ12と集束レンズ14との結合体を適合させることができる。20

【0035】

また別の実施形態において、ミラー16をプリズム表面とすることができます。装置の他のコンポーネントは、図1aから1dで先に説明され、示された装置にしたがうことになる。

【0036】

光路を、直線、彎曲線、及び曲線とし得ることもまた当然である。さらに、光路を、長さ、幅及び高さを有する3次元光路とすることができる。走査運動（すなわち、動径、直線またはヘリカル走査）に依存して、その上に焦点が乗る面の方位も変化し得る。さらに、光路は1つの光放射源または複数の光放射源（すなわち、複数の光源またはそれが光を伝送する複数本のファイバ）からの光を含むことができる。30

【0037】

次に図2b及び2cを参照すれば、多束単一モードファイバ10からなるファイバ束チップ12の拡大図が示される。多束単一モードファイバ10のそれぞれのファイバは、直径が、例えば、それぞれ5μm及び40μmの、コア10b及びその周りのクラッド層10aからなる。多束単一モードファイバ10のそれぞれの末端は、それぞれのファイバを通る光の焦点が間隔をあいて配されるように、40μmずつ段差を付けることができる。但し、40μm以外の段差を用いることもできる。

【0038】

次に図3を参照すれば、ファイバ束チップ12における、多束単一モードファイバ10のそれぞれのファイバについて、A-走査が、2mmの画像化深度のほぼ全体にわたってとられるが、ビーム径がほぼ最小（参照数字34に示される）であって軸上の位置に対して実質的に変化しない、それぞれのファイバの焦点近傍におけるほぼ40μmの短い軸方向範囲だけにとどめられる。本例の構造における、この40μmという範囲は、参照数字31で示される。A-走査は、ファイバ束チップ12内の多束単一モードファイバ10のそれぞれのファイバにより同時に行われる。事実上、多重A-走査は様々な動径方向において試料組織内の2mmの深度全体をカバーするが、多束単一モードファイバ10のそれぞれのファイバについては、40μmの焦点深度31に対応するそれぞれのA-走査区画だけが画像の構成に用いられる。焦点域31に示されるように、ビーム21b, 22b及び23bのそれぞれは、焦点38, 37及び36について明瞭な“砂時計”形を既知の態様4050

で示す。ビーム 21b, 22b 及び 23b のそれぞれに対して、遠視野ビーム広がりが線 32 で示され、近視野ビーム広がりが線 34 で示される。

### 【0039】

ミラー 16 を回転させる目的は、B - 走査（すなわち図 1 の走査領域 28 の）画像を生成するために、A - 走査方向に垂直な方向における動径（すなわち横方向）走査を生じさせることである。得られる、多束単一モードファイバ 10 の個々のファイバの焦点の動径走査パターンが、図 4 に示される。ミラー 16 の開豁面が B - 走査画像がとられるべき位置 “A” 及び “C” の方向に実質的に向けられているときにだけ連続走査面が存在することは、注目に値する。動径走査パターン上の他の位置においては、個々の A - 走査間の “デッドスペース” が非常に大きいため、組織の十分なサンプリングができない。したがって、本発明は、2 mm × 2 mm の画像が得られる範囲内で、実質的に “A” または “C” 位置において、約 20° のセクター角でセクター走査を行うために、セクター走査画像化装置を備える。本例においては、与えられた形状寸法により、セクター角をさらに大きくすると適切な断層画像を形成するには大きすぎる “デッドスペース” が生じるであろう。10

### 【0040】

図 4b および 4c はそれぞれ、ビーム焦点 36, 37 及び 38 を平面図及び端面図で示す。図示されるように、また先に示した図に対応して、個々の焦点 36, 37 及び 38 は軸 20 に垂直な動径平面において間隔がとられている。図 4c に示されるように、軸 26 に沿う端面図において、焦点 36, 37 及び 38 は深度に関して間隔がとられているが、重なり合って連続走査面すなわち走査領域 28 を形成している。20

### 【0041】

走査面すなわち走査領域 28 に垂直な、図 4a で “B” 及び “C” で表示される位置の方向に、実質的にミラー 16 の開豁面が向けられると、図 4d（パターンの平面図）及び図 4e（パターンの側面図）に示されるパターンが得られる。ここで、焦点は参照数字 40, 41 及び 42 で表示される。図 4d に示されるように、焦点 40, 41 及び 42 はそれぞれ、ファイバ束チップ 12 におけるファイバ間隔に対応する間隔がとられる、個別の面 40', 41' 及び 42' にある。面 40', 41' 及び 42' は軸 20 に垂直である。図 4b から 4e において、矢印 44 は動径走査方向を示す。20

### 【0042】

図 1d に示される直線並進システムについては、“デッドスペース” がなく、したがって直線並進システムは大きさがほぼ 2 mm × 2 mm の画像に適する画像化を行うことができる。30

### 【0043】

内視顕微鏡システムの例示的構成においては、生体内画像化に対して、生理学的運動による組織運動の最大速度を 5 mm / 秒に選んだ。近回折限界集束レンズ（すなわち、非常に小さな焦点を結ぶことで理想レンズに近いレンズ）を集束レンズ 14 として選んだ。近回折限界集束レンズはメレス・グリオ社（M e l l e s G r i o t I n c . ）から入手した。さらに、複数の単一モードファイバ 10 のそれぞれの単一モードファイバには、コア径が 5 μm（すなわち  $n_c \sim 5 \mu m$ ）であり、動作波長が 0.86 μm のファイバを用いた。さらに、本構成では、ほぼ  $n_c = 1.447$  のコア屈折率及び  $n = 0.005$  のコア - クラッド層間屈折率差を組み入れている。これらの値を用いれば、ファイバの NA は式（1）：40

#### 【数 1】

$$NA = n_c (2\Delta n)^{1/2} = 0.145$$

で与えられ、ファイバの許容角  $\theta_a$  は式（2）：

#### 【数 2】

$$\theta_a = \sin^{-1}(NA) = 8.32^\circ = 0.145 \text{ ラジアン}$$

で与えられる。50

## 【0044】

本構成ではさらに、複数本の単一モードファイバ10からの光を集束するために用いられる、倍率1対1及び遠視野ビーム発散角が<sub>a</sub>と同等の、理想レンズの概念を導入する。したがって、中心波長が<sub>0</sub>の光ビームに対して、焦点におけるビーム径<sub>f</sub>は式(3)：

## 【数3】

$$\phi_f = 2w_0 = 2 \frac{\bar{e}_0}{\delta e_a} = 3.95 \text{ mm} \approx \phi_c$$

で与えられる。スポット径<sub>f</sub>はコア径(<sub>c</sub>=5μm)とほぼ等しく、よって効率的な光結合が得られる。焦点深度は $2(w_0^2/\bar{e}_0) = 27.2 \text{ mm}$ であり、焦点36, 37及び38に対する焦点域の末端におけるビーム径<sub>f'</sub>は式(4)：

## 【数4】

$$\phi_{f'} = 2\sqrt{2}w_0 = 5.59 \text{ mm}$$

で与えられる。パラメータ<sub>f</sub>及び<sub>f'</sub>は軸方向における焦点位置の40μmの範囲内における振幅に関して定められるから、光強度(すなわち光振幅の2乗)に基づくビーム径は、実際上、5μmより小さくなり得る。

## 【0045】

上記の計算は主光軸上で有効な理想光学に基づく。<sub>c</sub>=5mm, <sub>f</sub>=5mmで作動距離が8.2mmの、市販のレンズ系を用いれば、2mm×2mmの画像をカバーするに必要なオフアクシス角は約5°であることが市販のレイトレーシングソフトウェアを用いてわかった。集束レンズ14のフィルファクターをほぼ80%としたレイトレーシング結果は、オンアクシス RMS 焦点が半径5.3μmにあり、5°オフアクシス RMS 焦点が半径10.3μmにあることを示す。特注レンズ系はより優れた性能を有するはずである。

## 【0046】

図1に示されるように、全光学系の作動距離、すなわち集束レンズ14から装置の焦点までの距離は、レンズ系の焦点距離、集束レンズ14の直径及び集束レンズ14とミラー16との間の間隙長により定まる。上で論じた市販レンズ系を用いれば、作動距離は約2.35mmである。画像の中心からミラー16の回転軸までの距離は約5.47mmである。動径方向で2mmの走査を達成するためには、セクター走査角は、光学系の形状寸法により定まり、ほぼ±10.4°、すなわち全体で約20°になるはずである。

## 【0047】

現時点で既存の生体内OCTシステムは、生物学的に許容し得る毎秒4ないし8フレームを得るために4ないし8回転/秒(RPS)で動径走査を行う。本実施形態の構成については、回転速度として4.4RPSが選ばれる。回転速度はA-走査の繰返しレート及び5μmの横方向解像度を得るに必要なA-走査回数に依存する。したがって、本発明の装置の画像化速度は4.4フレーム/秒であるが、様々なエンドユーザの用途によっては別の画像化速度が選択されることもあり得る。個々のフレームのそれぞれの画像化時間は、回転速度及びセクター走査角により定まり、12.6ミリ秒である。したがって、与えられたフレームに対して、システムは12.6ミリ秒間信号を取得し、その間にデータ処理が行われるフレーム間時間は約215ミリ秒である。これらのパラメータは、本システムに用いられる(後に説明される)光遅延発生器の性能に依存する。

## 【0048】

上記の計算は光波長860nmで動作する光源及び特注単一モードファイバに基づいてなされたが、1300nmのような別の波長で動作する光源及び市販ファイバを用いる実施態様も可能であり得る。図5aは、波長1300nmで動作する、市販ファイバ(コーニング(Corning)SMF-28)を用いた、この5チャネルファイバ束チップに対するビームスポット図を示す。ファイバ束チップのファイバ段差は125μmである。これらのファイバからの光ビームは、直径が5mmで焦点距離が4.5mmのレンズにより

集束されて、ほぼ 0.65 mm の焦点域をカバーする。得られる横方向画像化分解能はほぼ 10 μm である。図 5 b は、波長 890 nm で動作する、コア径が 5 μm でクラッド層径が 40 μm の特注ファイバを用いた、15 チャネルファイバ束チップに対するビームスポット図を示す。このファイバ束チップのファイバ段差は 40 μm である。中央の 5 チャネルのビームスポットだけが示される。得られる横方向画像化分解能はほぼ 0.65 mm の焦点域にわたりほぼ 5 μm である。

#### 【0049】

図 5 c は、図 5 a の 5 チャネルファイバ束チップに対する、ビームスポット径対焦点域に沿う距離を示す。図 5 c は、0.65 mm の焦点域全体にわたりビームスポット径が一様に 15 μm より小さいことを示す。図 5 d は、図 5 b の 15 チャネルファイバ束チップに対する、ビームスポット径対焦点域に沿う距離を示す。図 5 d は、0.65 mm の焦点域全体にわたりビームスポット径がほぼ 5 μm であることを示す。

#### 【0050】

次に図 6 を参照すれば、本発明の装置の基本光学素子の概略の全体的レイアウトには、複数の光源 50、複数のツリー型結合器 52、複数の 3dB 結合器 54、ファイバ束チップ 56、複数の検出器 58、複数の復調器 60 及び光遅延発生器 64 が含まれる。レーザとすることができる複数の光源 50 は、複数のツリー型結合器 52 に結合される。チップ 56 のファイバ(すなわちチャネル)のそれぞれに十分な光を確実に与えるためには 1 つより多くのレーザが必要となり得る。ツリー型結合器 52 のそれぞれは複数の 3dB 結合器 54 の内のいくつかにそれぞれの光源 50 を結合する。複数の 3dB 結合器 54 は、複数の光源 50 からの光のほぼ 1/2 を前方に伝送するためにファイバ束チップ 56 に結合される。ファイバ束チップ 56 は図 1 のファイバ束チップ 12 及びその他の光学素子(すなわち、集束レンズ 14 及びミラー 16)を備える。複数の光源 50 からの光のもう一方の 1/2 は検出器 58 に後方反射され、検出器 58 は続いて、サンプリングされたデータを処理して B - 走査画像 30 を生成するために機能する、コンピュータ 62 に復調器 60 を介して結合される。光遅延発生器 64 は、遅延反射信号を検出器 58 に与えるために、3dB 結合器 54 により用いられる。チップ 56 で検査されている試料は参考数字 65 で表示される。

#### 【0051】

図 6 に示されるレイアウトにおいては、3dB 結合器 54 の代わりに、1dB または 10 dB 光結合器等を用いることができる。さらに、ツリー型結合器 52 により 3dB 結合器 54 のそれぞれに、したがってそれぞれのファイバに伝送される光の強度は同じである必要はなく、実際には、3dB 結合器がファイバ(すなわちチャネル)に深い組織内走査を容易にする光を与えるかまたは浅い組織内走査を容易にする光を与えるかに依存して選ばれる。組織内深くを走査するためには高強度光が必要である。したがって、組織内深くを走査する光をファイバに送るツリー型結合器 52 及び 3dB 結合器 54 は、より多くの光を与えるように適合される。

#### 【0052】

図 7 a 及び 7 b は光遅延発生器 64 をさらに詳細に示す。既存の生体内 OCT システムにおけるものと同様の光遅延発生器 64 は、個別のファイバのそれぞれのコヒーレンスエンベロープを用いる A - 走査を行うために用いられる。光遅延発生器 64 は、回折格子 66、レンズ 67、走査ミラー 68 及びミラー 69 を備える。高速深度走査は、ファイバ束チップ 12 の多束単一モードファイバ 10 からの擬单色光を回折格子 66 上に分散させ、分散光を振動ミラー 69 上に集束させることによって、光遅延発生器 64 により達成できる。このことは、G. J. ティアニー、B. E. ブーマ及び J. G. フジモト(「回折格子ベース位相制御線による高速位相及び群遅延走査」, Nature Medicine, 1998 年, 第 4 卷, 第 7 号, p. 861 ~ 865)により説明されるように、周波数すなわちフーリエドメインにおいて線形ランプを印加する効果を有する。回折格子 66 における反射波長の再結合により、実空間時間遅延がつくられる。走査ミラー 68 の角度が数° の範囲の回転により急速に振動して基準アームにおける時間遅延を急速に変化させ、試

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料の高速繰返し深度操作を可能にする。

【0053】

多束単一モードファイバ10の内の1本のファイバからの光70が図7aに示される。光70は、回折格子66により、スペクトル成分71, 72及び73で表されるスペクトル成分に分散される。スペクトル成分71は光70の最短波長を表し、スペクトル成分73は光70の最长波長を表し、スペクトル成分72は光70の中心波長を表す。光70のこれらのスペクトル成分は光遅延発生器64内で垂直方向に配列される。同様な態様で、多束単一モードファイバ10の他のファイバからの光も分散され、それぞれのファイバからの分散光には垂直方向に間隔がとられて、垂直方向に配列される。多束単一モードファイバ10のそれぞれのファイバからの分散光の位相変調を容易にする、与えられたファイバについての、走査ミラー68のピボット軸からの分散光の中心波長のオフセットは $x_d$ で表わされる。あるいは、 $x_d$ がゼロである場合には、多束単一モードファイバ10のそれぞれのファイバからの光を位相変調するため、多束単一モードファイバ10のそれぞれのファイバに対して位相変調器が必要になる。このことには、走査ミラー68の大きさを縮小でき、したがってより高いフレームレートを用い得るという利点がある。さらに、位相変調器は電気的に制御され、よって非常に安定な信号が生成され得る。

【0054】

次に図7bを参照すれば、多束単一モードファイバ10のそれぞれのファイバからの分散光が走査ミラー68上に75, 76, 77及び78のように縦列をなして垂直方向に配置されるように、多束単一モードファイバ10がファイバ束チップ12に配列される。あるいは、横列のような、別の順序配置を多束単一モードファイバ10のそれぞれのファイバからの光のスペクトル成分に対して用いることもできる。

【0055】

図6に示されるように、单一の光遅延発生器を多束ファイバに遅延を導入するために用いることができる。单一の光遅延発生器に結合され得るチャネルの数の決定における制限要因は走査ミラーの物理的大きさであり、したがってチャネル数は光遅延発生器の共鳴周波数により制限される。市販の共鳴光走査器は16kHzまで動作可能である。したがって、4mm×5mmの大きさの走査ミラー68を用いることができる。ファイバ束アレイの大きさは約2mmであるから、1つの光遅延発生器にアレイ全体を適合させることができる。したがって、本発明の実施形態に対し、光走査角 $\theta$ を±2°として、 $f_r = 16\text{ kHz}$ で動作する光走査器を有する单一の光遅延発生器が用いられる。本実施形態には、ピッチが $p = 3.33\mu\text{m}$ 、中心周波数が $f_0 = 0.86\mu\text{m}$ 、焦点距離が $f_1 = 21\text{mm}$ の回折格子も組み込まれる。したがって、自由空間群光路長差 $\Delta l_g$ は式(5)：

【数5】

$$\Delta l_g = 4\alpha \left( f_r \frac{\lambda_0}{p} - x_d \right) = 0.618\text{mm}$$

で与えられ(ローリンズ等(1998年)による)、またピーク対ピーク値は1.24mmである。式(5)において、 $x_d = 1\text{mm}$ は $\theta$ スペクトル線と共にミラーのピボット軸との間の変位である。ピークA-走査速度 $V_A$ 最大は式(6)：

【数6】

$$V_{A\text{最大}} = 2\pi\Delta l_g f_r = 62.1\text{m/s}$$

で与えられ、A-走査速度 $V_A$ は式(7)：

【数7】

$$V_A = V_{A\text{最大}} \cos(2\pi f_r t)$$

にしたがって変化する。コヒーレンス長 $l_c$ が5μmでガウス型発光スペクトルをもつ光源を選べば、等価発光帯域幅 $\Delta\lambda$ は式(8)：

【数8】

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$$\Delta\lambda = \beta \frac{\lambda_0^2}{l_c} = 98\text{nm}$$

で与えられ、ここでガウス型エンベロープに対しては  $b = 0.66$  である。

【0056】

共鳴ミラーの大きさが次に決定される。一次回折を有する回折格子をもつ光遅延発生器に対して、回折角  $(\theta)$  は式(9)：

【数9】

$$\theta(\lambda) = \sin^{-1}(\lambda/p)$$

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で与えられる。レンズのフーリエ面における  $(0^- / 2)$  から  $(0^+ / 2)$  までのスペクトルの広がり  $\times$  は式(10)：

【数10】

$$\Delta x = 2f_l [\theta(\lambda_0 + \Delta\lambda/2) - \theta(\lambda_0 - \Delta\lambda/2)] = 1.3\text{mm}$$

で与えられる。

【0057】

ミラー幅は 4 mm であるから、変位  $x_d$  の値をほぼ 1 mm として共鳴ミラーの一辺上にスペクトルを適合させることができる。このことが図 7 a 及び 7 b に示されている。システムの個々のチャネルのキャリア周波数  $f_c$  は式(11)：

【数11】

$$f_c = (4x_d \alpha \cdot 2\pi f_r / \lambda_0) \cos(2\pi f_r t)$$

で与えられ(ローリンズ等(1998年))、最大で 16.3 MHz である。

【0058】

干渉像(すなわち干渉縞パターン)の帯域幅  $f$  は式(12)：

【数12】

$$\Delta f = \frac{\Delta\lambda}{\lambda_0^2} \cdot 4\pi\alpha f_r \cdot 2(f_l \lambda_0 / p - x_d) \cos(2\pi f_r t)$$

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で与えられ、最大で 8.4 MHz である。

【0059】

$f_c(t) > f(t)$  であるから、急峻な周波数カットオフは必要であるが、通常の整流及び低域フィルタ方式によって適切な復調を行うことができる。(単一チャネルで行われる A - 走査深度)  $D_A = 40 \mu\text{m}$  が最高キャリア周波数に一致し、よって  $D_A$  にわたるキャリア周波数変動が最小化されるように、システムの個々のチャネルを設定することが好ましい。キャリア周波数は時間に関して正弦的に変動し、変動  $f_c$  は式(13)：

【数13】

$$\Delta f_c = f_c \left\{ 1 - \cos \left[ \sin^{-1} \left( D_A / \Delta l_g \right) \right] \right\} = 34\text{kHz}$$

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によって与えられ、 $f_c$  の約 0.2 % である。

【0060】

別の位置においても、信号を適切に復調することはできるが、キャリア周波数の変動はより大きくなるであろう。信号を復調するため、アナログ高速整流器及び 10 極低域フィルタを復調器 60 に組み込むことができる。実際には、信号の中心が DC にかけ、帯域幅が  $f$  になるように、信号周波数が下方偏移される。復調エンベロープ信号は次いで適切なサンプリングレートでデジタル化される。現時点では既存のデータ取得(DAQ)カードは、約 60 dB の SNR(信号対雑音比)で、毎秒 30 メガサンプル(MS/s)で動作する。 $f = 8.4 \text{MHz}$  の干渉像スペクトルに対してガウス型形状を選べば、60 dB 点は約 14.5 MHz にある。したがって、そのような信号のデジタル化に対するナイキ

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ストレートはほぼ 29MS / 秒である。したがって、現時点で既存のDAQカードはエイリアシングを生じずにエンベロープ信号をデジタル化できるであろう。

#### 【0061】

最高キャリア周波数においてエンベロープ信号をデジタル化するためのサンプリングレートを 30MS / 秒とすれば、軸方向における空間サンプリング間隔は  $\Delta_{\text{軸方向}} = V_{\text{A最大}} / S = 2.07 \mu\text{m}$  である。試料を通って上下を繰り返す A - 走査を示す走査経路 80 が図 8 に示される。サンプリング点が参照数字 82 で表示される。2.07 μm の軸方向間隔が参照数字 84 で表示される。横方向における空間サンプリング間隔は、横方向すなわち B - 走査速度及び光遅延発生器 64 の光走査器の共鳴周波数により決定される。ミラーの回転軸からの動径距離  $r$  が 5.47 mm である画像の中心において、動径サンプリング間隔  $\Delta_{\text{動径}}$  は式(14) :

#### 【数14】

$$\Delta_{\text{動径}} = V_{\text{動径}} / 2f_r = 2\pi\Omega r / 2f_r = 4.73 \mu\text{m}$$

により与えられる。図 8 に、この間隔が参照数字 86 で表示される。最浅深度を走査するファイバについての横方向空間サンプリング間隔は 3.86 μm であり、最深チャネルについての横方向空間サンプリング間隔は 5.59 μm である。したがって、画像中心における画素寸法は、軸方向 2.07 μm × 横方向 4.73 μm である。横方向画素寸法は画像の深度にわたって 3.86 μm から 5.59 μm まで変化する。ミラー 16 の回転速度を変えることにより、フレームレートを犠牲にして、横方向サンプリング間隔を変えることができる。共鳴周波数がより高い光走査器を用いても、サンプリング間隔を縮小することができます。

#### 【0062】

パルス光源(例えば波長 860 nm で発光する 15ないし 20 フェムト秒パルスレーザ)に対しては、コヒーレンス長はほぼ 4.5 μm ないし 6 μm であろう。軸方向空間サンプリング間隔は約 2 μm であり、これはコヒーレンス長の 1/2 より小さいから、画像は軸方向で問題なくサンプリングされる。集束レンズ 14 として近回折限界集束レンズを用いれば、ビームスポット径は約 5 μm になるはずである。横方向空間サンプリング間隔が 3.86 μm から 5.59 μm まで変化するから、ビームウエスト径が約 5 μm であるとすれば、画像の分解能はサンプリング分解能を若干下回る。しかし、空間サンプリング間隔は最終画像分解能と等価ではなく、最終画像分解能は局所的コントラスト及び雑音レベルの影響も受ける。局所的コントラストは画像において隣接画素として表れる試料の 2 点の間の反射率の差である。これらの 2 つの点の反射率が同様であれば、すなわち局所的コントラストが低ければ、これらの点を分解することは困難であろう。

#### 【0063】

画像化速度は運動ぶれを小さくするに十分に高速であるべきである。標的速度(すなわち組織運動)が一般に 5 mm / 秒であるとすれば、1 フレーム時間(経過時間 12.6 ミリ秒)内に標的是特定の方向に 63 μm まで移動することができ、これは 5 μm の設計分解能よりかなり大きい。本実施形態においては、コヒーレンスゲートを 40 μm の距離にかけて走査するに必要な時間である 0.6 マイクロ秒内に画像の 1 本の線が形成されるようにして、A - 走査が全てのチャネルにおいて同時に行われる。2 つの連続する A - 走査間の時間は、システムのミラー 16 の回転速度及び 1 画像当りの A - 走査数で定まる、約 1.6 マイクロ秒である。すなわち、1.6 マイクロ秒間の移動量は 0.08 μm であり、これは分解能よりかなり小さいから、得られる画像は鮮明になるはずである。したがって、画像には運動ぶれがないはずであるが、それでも運動アーティファクトは存在し得る。生じる運動アーティファクトはおそらく、組織構造の寸法及び標的速度に依存して 63 μm もの大きさになり得る、画像化される組織構造の形状寸法上の変形であろう。この運動アーティファクトは、空気 - 組織界面が複数の光源 50 からの光に及ぼす効果による。

#### 【0064】

図 9 に示されるように、画像化される組織内部の、装置の個々のファイバの焦点は、組織

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内の焦点の位置の距離  $d_0$ 、組織表面の屈折率が 1 であるか否か、及び（一般にほぼ 1.4 である）組織の実屈折率にしたがって変化し得る。したがって、実焦点は組織表面下の距離  $d_f$  にあり、 $d_f$  は式（15）：

## 【数 15】

$$d_f = d_0 \cdot \frac{\tan \theta_1}{\tan \theta_2} = d_0 \cdot \frac{\tan \theta_a}{\tan \left[ \sin^{-1} \left( \frac{n_1}{n_2} \cdot \sin \theta_a \right) \right]}$$

で与えられる。ここで、 $\theta_1$  は個々のファイバの許容角  $\theta_a$  に等しいとされ、 $\theta_2$  は組織外部（すなわち空気）の屈折率  $n_1 = 1$  及び組織内部の屈折率  $n_2 = 1.4$  により定まることになる。

## 【0065】

コヒーレンスゲート位置  $d_c$  は式（16）：

## 【数 16】

$$d_c = \frac{n_1}{n_2} \cdot d_0$$

にしたがって変化する。したがって、光の進行速度は媒質の屈折率が大きくなるほど遅くなるという事実により、 $n_1 = 1$  の（すなわち組織が存在しない）媒質内では一致する、焦点と光ビームのコヒーレンスゲートとの間に、光路の不一致が存在する。この不一致の大きさ  $d$  は式（17）：

## 【数 17】

$$\Delta d = n_2 (d_f - d_c) = \frac{n_2 d_0 \tan \theta_a}{\tan \left[ \sin^{-1} \left( \frac{\sin \theta_a}{n_2} \right) \right]} - d_0$$

で表される。組織の屈折率  $n_2 = 1.4$  から、 $d = 0.97 d_0$  が得られる。この不一致問題は高NA-OCMシステムに対して共通であり、既存の高NA-OCMシステムの多くは何らかの形態の動的補償、すなわち基準光路長を動的に変えることによる  $d$  の補償を用いるが、高画像化速度でのそのような動的補償は困難である。したがって、本発明の実施形態の一態様は、検出された干渉像信号の‘適応トリガ印加’を用いることである。

## 【0066】

上に示したように、自由空間群光路長差はピーク間で  $2 l_g = 1.24 \text{ mm}$  であり、これは  $40 \mu\text{m}$  でしかない有用な A-走査範囲よりかなり大きい。このため、コヒーレンスゲートが焦点を通過するときにだけトリガをかけて干渉像を得ることができるから、上記の不一致を処理する余裕が残される。

## 【0067】

図9に示されるように、それぞれのファイバチャネルに対する作動距離  $d_w$  は  $n_2$  にしたがって変化するが、 $n_2$  はほぼ一定である。したがって、どこに組織表面があるかがわかれれば、 $d_0$  を決定することができ、続いて  $d$  を決定することができる。

## 【0068】

組織表面の斜視図及び任意の軸線 90 を示す図10を参照すれば、組織表面を走査するように指定されたチャネル 1 が、走査領域 28 において軸線 90 を最初に通過するチャネルである。チャネル 1 及び 2 の焦点が、軸線 90 を通過する多束単一モードファイバ 10（すなわち複数のチャネル）からの光の概略表示 94 に参照数字 91 及び 92 で表示される。最終チャネル、すなわち本例ではチャネル 50 の焦点は参照数字 95 で表示され、画像における最深層を走査するように指定される。表示 94 の全体のプロファイルは、その範囲内ではコヒーレンスゲートと焦点距離を一致させることができる、適応トリガ域を定め

る。50のチャネルの内の1つ、すなわちチャネル“v”は、空気-組織界面が擬似的にミラーとしてはたらき、入射光を反射するから、強く判然とした正反射を受けることになる。組織表面の下では、組織が入射光を散乱させ、吸収する混濁媒質としてはたらく。すなわち、チャネル“v”が、チャネル“v”より前のチャネルは全て雑音レベルにある信号を返すであろうから、この特定の軸線90に対する $d_0$ を決定するであろう。したがって、“適応トリガ印加”法は‘隣りの’チャネルに比較して反射の大きな増加があるチャネルを識別することにより組織表面の位置を突き止めるために、隣接するチャネルについて検出された反射光を比較するステップを含む。次いでこの情報が引き続くチャネルのそれぞれに順次伝えられ、焦点とコヒーレンスゲートとの間の不一致を小さくするために、それぞれのチャネルに対するトリガ点が前記情報にしたがって設定される。

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## 【0069】

例として、チャネル“v”が13チャネルであれば、チャネル1から12は組織表面より上の自由空間の走査に設定され、チャネル13は組織表面の走査に設定され、引き続くチャネルは、それぞれのチャネルの光ビームの焦点とコヒーレンスゲートとの間の不一致は生じずに組織内部の走査に設定されるように、装置が較正される。画像化の間、図10に参照数字96で表示されるように、組織表面の位置について  $d_0 = \pm 0.5 \text{ mm}$  の許容範囲を設けることができる。この許容範囲は、次に説明されるように、A-走査性能及びエンベロープ検出器の周波数応答に關係する。

## 【0070】

$d_0 = 0.5 \text{ mm}$  とすれば、補償を必要とする不一致  $d'$  は式(18)：

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## 【数18】

$$\Delta d' = 0.693 \times 0.5 = 0.347 \text{ mm}$$

で与えられる。このことは、最高キャリア周波数において干渉像信号をトリガする代わりに、実キャリア周波数  $f_c'$  が式(19)：

## 【数19】

$$f_c' = f_{c\text{最高}} \cos(\sin^{-1}(\Delta d'/\Delta l_g)) = 13.5 \text{ MHz}$$

で与えられなければならないことを意味し、この実キャリア周波数は最高キャリア周波数の約83%であり、これにともなって干渉像信号帯域が変わる。エンベロープ検出器の周波数応答は動的に調整できるとしても、エンベロープ検出器の応答は固定するが、カットオフ周波数に17%の許容差をもつように設計する方が、より簡単であり、高速である。このようにすれば、適応トリガ印加方式全体が固定型コンポーネントだけを含み、補償の全てが電気的に行われて高速画像化要件を満たす。

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## 【0071】

図6に示される光コンポーネントは、以下のように選ぶことができる。S.A.ボッパート, B.E.ボウマ, C.ピトリス, J.F.サザーン, M.E.ブレジンスキー, 及びJ.G.フジモト(「生体内細胞光コヒーレンス断層撮像」, Nature Medicine, 1998年7月, 第4巻, 第7号, p. 861~865)に基づけば、ほぼ2mmないし3mmの深度までの画像化を可能にするために、2mWの組織入射パワーを用いる非内視鏡OCTシステムにおいて、100dBをこえるSNRを達成することができる。用いられた光源は、コヒーレンス長が5.1μmの、中心波長1280nmで動作する、カーレンズ-モードロック固体Cr<sup>4+</sup>:フォルステライトレーザである。しかし、本発明の実施形態はこのタイプの光源にも、広帯域超発光ダイオードのような、その他のいかなるタイプの光源にも限定されない。例えば、別の可能性には、ほぼ4.5μmないし6μmのコヒーレンス長を提供するであろう、860nmを中心としてほぼ100nmの帯域をもつ、白色発光Cr:LiSAF光源がある。このダイオードポンピング型モードロック固体レーザは、860nmで動作させたときに、繰返レート約100MHz及び平均パワー30mWで動作するはずである。パルスエネルギー変動は1%未満になるはずである。図6に参照数字50で表示される、いくつか(例えば2つまたは4つ)の上記レー

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ザは、50チャネルの所要パワーを全て供給する必要がある。組織のより深い部分を走査するチャネルにはチャネル当たりほぼ1ないし2mWの入射パワーが必要であろうし、より浅い部分を走査するチャネルにはそれほどのパワーは必要ではないであろう。ツリー型結合器52は、光源パワーを上記要件に合せて分割するように構成することができる。最高キャリア周波数は16.3MHzであるから、それぞれの干渉縞は少なくとも6つのレーザパルスを含むであろう。したがって干渉縞パターンは十分にサンプリングされるはずである。

#### 【0072】

それぞれのチャネルに対して、個別の光受信器すなわち検出器58を用いて、干渉縞を検出することができる。最大検出器帯域幅は125MHzであるが、本発明の装置では、検出器帯域幅は、キャリア周波数及び干渉像の帯域幅により定まるように、30.8MHzで十分であり得る。

#### 【0073】

本発明の代替実施形態は、装置の複雑性を軽減し、コストを低減するために光コンポーネントを共有するという概念に関わる。図11aを参照すれば、干渉像のAC成分が干渉像のDC成分から分離されてAC成分だけが増幅される、一般的な平衡検波型単チャネル干渉計150が示される。単チャネル干渉計150は、光ファイバ及び3dB結合器140, 142及び144のネットワークを介して接続される、広帯域IR(赤外)光源L, 可視波長案内光G, 平衡検波器BD, 偏光制御器PC, 位相変調器MOD及び光遅延発生器ODGを備える。“x”はファイバネットワークのデッドエンドを表す。可視波長案内光Gは単チャネル干渉計150が指し示している方向を示す(すなわち画像化される方向を示す)緑色レーザとすることができる。単チャネル干渉計150は試料Sに結合される。

#### 【0074】

図11aの構成を拡張して、図11bに示されるような、2チャネル干渉計160を構成することができる。下付添字は2本のチャネルにおけるコンポーネントを表す。下付添字のないコンポーネントはそのコンポーネントが両チャネルに用いられていることを示す。2チャネル干渉計160は、レーザL', 可視波長案内レーザG', 2対1ツリー型結合器TC1, 偏光制御器PC<sub>1</sub>, PC<sub>2</sub>及び位相変調器MOD', 可変遅延素子VD<sub>1</sub>及びVD<sub>2</sub>, 光遅延発生器ODG', 検出器BD<sub>1</sub>及びBD<sub>2</sub>, 並びに3dB結合器162, 164, 166, 168, 170及び172を備える。可変遅延素子VD<sub>1</sub>及びVD<sub>2</sub>はそれぞれのチャネルに対してコピーレンズゲート位置を調節するために組み込まれる。2本のチャネルは、組織試料の相異なる位置にある2つの点とすることができます、試料S<sub>1</sub>及びS<sub>2</sub>に結合される。本例において、光源L'は2本のチャネル間で共有され、チャネル1の光パワーはチャネル2の光パワーの2倍である。したがって、チャネル1はチャネル2より深い組織領域を走査するために用いられるべきである。2対1ツリー型結合器TC1は、両チャネルが(位相変調器MOD'及び光遅延発生器ODG'を含む)同じ基準アームを共有できるように用いられる。同じ基準アームを共有できるという能力により、1つの位相変調器を多束單一モードファイバ10(すなわち全チャネル)からの光の位相変調を行うために用いることができる。2本のチャネルからの光がツリー型結合器TC1により1本のファイバに結合されて同じ位相変調器MOD'に送られることに注意されたい。したがって、2チャネル干渉計160のコストが低減され、複雑性が軽減される。

#### 【0075】

図11bに基づけば、汎用光ネットワークを図11cに示される光ネットワーク180のようなNチャネルOC-Tシステムを構成するために用い得ると考えられる。光ネットワーク180は、第nチャネル182のための光ネットワーク及びn本のチャネルの全てに共有される基準アーム184を備える。第nチャネル182のための光ネットワークは、検出器BD<sub>n</sub>, 3dB結合器194, 196及び198並びに偏光制御器PC<sub>n</sub>及び、試料S<sub>n</sub>に結合された、可変遅延素子VD<sub>n</sub>を含む試料アームを備える。第nチャネル182

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のための光ネットワークは、第(  $n - 1$  )チャネルから光源光 186 を受け取り、3dB 結合器 194 を介して光源光 188 を第(  $n + 1$  )チャネルに送り出す。第  $n$  チャネル 182 のための光ネットワークは、第(  $n - 1$  )チャネルから案内光パワー 190 を受け取り、3dB 結合器 196 を介して案内光パワー 192 を第(  $n + 1$  )チャネルに送り出す。本実施形態において、光源( 図示せず )は、等比級数的または別の適切なパワー分割方式にしたがうパワー配分により  $N$  本のチャネルのそれぞれの間で共有することができる。 $N$  対 1 ツリー型結合器  $TC_n$  , 位相変調器  $MOD$  " 及び光遅延発生器  $ODG$  " を含む基準アーム 184 は、 $N$  本のチャネルのそれぞれの間で共有される。

#### 【 0076 】

図 11a , 11b 及び 11c に示される構成図のそれぞれでは、検出器に結合された 3dB 結合器から送られる試料及び基準アームからの反射光の間の干渉による干渉パターンの光の一部が失われるという事実を問題としてかかえている。本例では、3dB 結合器が用いられているから、干渉パターンの光の 50 % が失われる。例えば、図 11a においては、干渉パターンの光の 50 % だけが 3dB 結合器 140 及び 142 から検出器 BD に送られる。このため、低強度の干渉パターンに対しては特に、干渉パターンの検出が一層困難になる。これを処理するため、光サーチュレータのような非相反光素子を、3dB 結合器だけが用いられた場合には失失していた部分光を検出器に送るために用いることができる。

#### 【 0077 】

図 12a , 12b 及び 12c を参照すれば、単チャネル OCT 装置 200 , 2 チャネル OCT 装置 210 及び、 $N$  チャネル OCT 装置 220 のための光ネットワークの、光サーチュレータを備える代替実施形態が示される。図 12a , 12b 及び 12c においては、検出のためにより強度の高い干渉信号を与えるため、干渉パターンの光を回収して検出器 BD , BD<sub>1</sub> , BD<sub>2</sub> 及び BD<sub>n</sub> のそれに導くため、光サーチュレータ C , C<sub>1</sub> , C<sub>2</sub> 及び C<sub>n</sub> が用いられる。3つの実施形態の残りのコンポーネントは、図 11a から 11c に示される、単チャネル OCT 装置 150 , 2 チャネル OCT 装置 160 及び、 $N$  チャネル OCT 装置 180 のための光ネットワークのコンポーネントと同様である。光を回収して回収光を検出器に与えるために光サーチュレータを用いるという概念は図 6 の装置にも適用でき、この場合、光サーチュレータは 3dB 結合器と検出器との間に配することができる。

#### 【 0078 】

図 11c 及び 12c に示される構成図によりエレガントな設計が導かれるが、コンポーネント( すなわち位相変調器 )を共有する並列干渉計では、非常に大きなチャネルクロストークを生じることがあり、そのようなクロストークは結果として画像劣化を引き起し得る。しかし、チャネル間のファイバ長を一致させないことで、クロストークを効果的に処理できる。電気的クロストークは標準的な遮蔽及び接地法を用いて処理できる。以下で光クロストークを説明する。

#### 【 0079 】

次に図 13a を参照すれば、チャネルクロストークを調べるために組み上げた 2 チャネル OCT システム 230 が示される。2 チャネル OCT システム 230 は、レーザ L<sub>E</sub> , 検出器 D<sub>1</sub> 及び D<sub>2</sub> , ビームスプリッタ BS<sub>1</sub> 及び BS<sub>2</sub> , 1 対 2 ツリー型結合器 TC<sub>E</sub> , 位相変調器 PM<sub>E</sub> , 光遅延発生器 ODG<sub>E</sub> , ビームコリメータ BC<sub>1</sub> 及び BC<sub>2</sub> , 並びに試料をシミュレートする 2 つのミラー S<sub>1</sub> 及び S<sub>2</sub> を備える。2 チャネル OCT システム 230 では、所望の画像化信号はチャネル 1 光路及びチャネル 2 光路からくる。チャネル 1 に対する所望の画像化信号は、光路：

$$L_E \quad BS_1 \quad S_1 \quad BS_1 \quad D_1 \quad ( 20 )$$

からの光が、光路：

$$L_E \quad BS_1 \quad ODG_E \quad BS_1 \quad D_1 \quad ( 21 )$$

からの光とコヒーレントに干渉するときに生じ、検出器 D<sub>1</sub> で検出される。チャネル 2 に対する所望の画像化信号は、光路：

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$L_E \quad B S_2 \quad S_2 \quad B S_2 \quad D_2$

( 2 2 )

からの光が、光路：

$L_E \quad B S_2 \quad O D G_E \quad B S_2 \quad D_2$

( 2 3 )

からの光とコヒーレントに干渉するときに生じ、検出器  $D_2$  で検出される。さらに、2本のチャネルにおけるOCT画像化は、 $B S_1 \quad S_1$  光路長が  $B S_1 \quad O D G_E$  光路長に等しく、 $B S_2 \quad S_2$  光路長が  $B S_2 \quad O D G_E$  光路長に等しいときに限りおきる。そうでなければ、上述した所望の画像化経路ではない2つ（またはさらに多く）の様々な経路からの反射光の強めあう干渉により画像劣化がおこり得る。

### 【 0 0 8 0 】

図13aに示される光ネットワークに基づけば、2種類の主要なクロストーク源があり得る。一次クロストーク源はおそらく、（ミラーまたは試料により）一方のチャネルのビームスプリッタから他方のチャネルのビームスプリッタ及び検出器に反射されるコヒーレント光であろう。そのようなクロストークは画像化信号強度に等しい強度を有し、おそらくかなりの画像劣化を生じさることになる。一方のチャネルから他方のチャネルへの反射は、光遅延発生器  $O D G_E$  あるいは試料  $S_1$  または  $S_2$  でおこり得る。したがって、光路：

$L_E \quad B S_1 \quad S_1 \quad B S_1 \quad D_1$

( 2 0 )

からの光が、光路：

$L_E \quad B S_2 \quad O D G_E \quad B S_1 \quad D_1$

( 2 4 )

からの光と干渉し得る。あるいは、光路：

$L_E \quad B S_2 \quad S_2 \quad B S_2 \quad D_2$

( 2 2 )

からの光が、光路：

$L_E \quad B S_1 \quad O D G_E \quad B S_2 \quad D_2$

( 2 4 )

からの光と干渉し得る。

### 【 0 0 8 1 】

試料アーム1及び2は通常、試料アームが組織試料の相異なる点（すなわち相異なる深度）に向けられるであろうから、図13aに示されるように分離されていることはないであろう。試料アームが分離されていない場合には、チャネル1からチャネル2に、及びこの逆に、反射がおこることになる。そのような場合には、光路：

$L_E \quad B S_2 \quad S_2 \quad B S_1 \quad D_1$

( 2 6 )

からの光が、光路：

$L_E \quad B S_1 \quad O D G_E \quad B S_1 \quad D_1$

( 2 1 )

からの光と干渉し得る。あるいは、光路：

$L_E \quad B S_1 \quad S_1 \quad B S_2 \quad D_2$

( 2 7 )

からの光が、光路：

$L_E \quad B S_2 \quad O D G_E \quad B S_2 \quad D_2$

( 2 3 )

からの光と干渉し得る。

### 【 0 0 8 2 】

ビームスプリッタ及びコネクタ挿入点のような望ましくない位置においても反射がおこり得ることを想起するべきである。そのような反射は、これらの経路からの光がかなりの強度を有する干渉縞を生じれば、画像雑音に寄与し得ると考えられる。しかし、この種の雑音は低強度であるから、おそらくは、先に説明したチャネルクロストークに対しては二次的であろう。

### 【 0 0 8 3 】

システムの解析により、そのような後方反射の干渉に対する最悪事態のシナリオにはコネクタからの一回反射が関わることが明らかになった。例えば、以下の光路：

$L_E \quad B S_1 \quad S_1 \quad B S_1 \quad D_1$

( 2 0 )

からの光が、光路：

$L_E \quad B S_2 \quad O D G_E \quad P M_E \quad O D G_E \quad B S_1 \quad D_1$

( 2 8 ) か

らの光と干渉し得る。

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## 【0084】

いざれか2つの経路からの光の干渉に対しては4つの帰結が考えられ、帰結は光路長差に依存する。第1に、光路長が同じであれば、検出器における干渉縞の強度は試料の反射率だけに基づく真の信号強度より高くなるであろう。この種の画像雑音は雑音として検出できず、画像全体にわたり測定される試料強度を変えることになる。幸いにして、光路長が正確に一致することはほとんどあり得ない。第2の可能性は、光路長が光源のコヒーレンス長の範囲内で一致し得ることである。この状況では、干渉縞エンベロープの幅が広がり、したがって軸方向分解能が低下することになるであろう。この状況はおこりそうもないが、鏡面深度プロファイルの半値幅を測定することにより検出できる。第3の可能性には、光源 $L_E$ のコヒーレンス長より大きく、光遅延発生器 $ODG_E$ の走査深度より小さい距離だけ異なっている、光路長が関わる。この状況は、光遅延発生器 $ODG_E$ による1回の深度掃引内の分離した2つのコヒーレンスエンベロープとして現れ得る。最後の、最もありそうな可能性は、光路長が光遅延発生器 $ODG_E$ の走査深度より大きく異なり、雑音すなわち無関係な干渉縞はシステムで検出されないであろうことである。

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## 【0085】

上記の一次型のチャネルクロストークは、ファイバ光学系の製作上おこりそうもないはずである。 $BS_1$   $ODG_E$  光路長及び $BS_2$   $ODG_E$  光路長は本質的に、ビームスプリッタ $BS_1$  及び $BS_2$  から至るファイバピグテイルの長さにより、あらかじめ定められる。 $BS_1$   $S_1$  光路長及び $BS_2$   $S_2$  光路長は計画的に、あらかじめ定められた対応する基準アーム長に一致させられる。一般的に製作されたファイバ長は数10mm異なっており、これは光遅延発生器 $ODG_E$ の走査深度より少なくとも1桁大きい。したがって、この種のクロストークが2チャネルシステムで問題となるはずはない。

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## 【0086】

挿入点反射の場合には、 $PM_E$   $ODG_E$  光路長が光路 $BS_1$   $S_1$  と光路 $BS_2$   $ODG_E$ との間の光路長差に一致すれば、干渉縞及び画像劣化が生じ得る。この場合も、ファイバ長が約300mmであり、一方光遅延発生器 $ODG_E$ の走査深度は2mmしかないから、この種の二次雑音はおこりそうもないはずである。さらに、そのような干渉縞強度はシステム雑音で見えなくなってしまうであろう。第2に、用いられる装置は最大で0.6dBの挿入損失（言い換えれば、最大で0.6dBの反射）を有し、したがって、そのような信号は図13aの構成に用いられる検出限界より小さい。

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## 【0087】

2本のチャネルに同じファイバ及び光コンポーネントを用い得ることを示すため、OCTシステム230を評価した。試料アーム光路長及び光遅延発生器 $ODG_E$  基準アーム光路長がそれぞれのチャネルで一致し、干渉縞列が検出器 $D_1$  及び $D_2$  のそれぞれで見られるように、試料アームミラー $S_1$  及び $S_2$  を配置した。位置合せのため及び光が、チャネル1からチャネル2を含むファイバに、及びこの逆に、反射する可能性を排除するため、試料 $S_1$  及び $S_2$  に対する試料アームは分離したままにした。光遅延発生器は位相変調及び群遅延のいずれの生成にも用いることができる（ティアニー等（1997年））が、図13aに示した構成では、光遅延発生器 $ODG_E$ を群遅延（すなわち深度走査）に用い、基準アームの位相変調器 $PM_E$ を位相遅延を生じさせるために用いた。

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## 【0088】

図13aの実験構成では、AFCテクノロジーズ社（AFC Technologies Inc.）製の1310nm, 9mW光源（モデルBBS1310）を、光源 $L_E$ に備えた。光源 $L_E$ の中心波長は1310nmであり、測定したスペクトル広がりは±40nmであった。測定した光源 $L_E$ のコヒーレンス長は10μmであった。検出帯域中心が1310nmにあり、帯域幅が100nm以上の、155Mbpsパーキン・エルマー（Perkin Elmer）InGaAs光ダイオード受信器を検出器 $D_1$  及び $D_2$  に用いた。JDSユニフェーズ（JDS Uniphase）43MHz位相変調器を位相変調器 $PM_E$ に用いた。ビームスプリッタ $BS_1$  及び $BS_2$  には、メトロテック（Metrotek）社製を用いた。ビームコリメータ $BC_1$  及び $BC_2$  には、オズ・オプティックス（Oz Optics）社製を用いた。

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OZ Optics)社製を用いた。上記またはその他の部品製造業者からの、代わりの適当なコンポーネントを用いることもできる。

#### 【0089】

光遅延発生器ODG<sub>E</sub>は、CVIスペクトラル・プロダクト(CVI Spectral Products)社製の1310nm用150本/mmプレーズド回折格子を用いて、コリメート光を分散させた。光を振動ミラー上に集束させるため、直径が30mmで焦点距離が100mmのメレス・グリオ社製ガラスダブルレットレンズを用いた。8kHzで動作し、±1°の機械角すなわち±2°の光学角にわたって走査する共鳴走査器には、EO PC(エレクトロ-オプティカル・プロダクト・コーポレーション(Electro-Optical Products Corporation))社製を用いた。この角度設定は試料S<sub>1</sub>及びS<sub>2</sub>に対する試料アームにおける約1mmの深度走査に対応する。走査深度は2本のチャネルの光路長の不一致に関して重要な要件である。例えば、光路長が1mmより大きく異なれば、2本のチャネル間のクロストークは最小になるはずであり、適切な遮蔽及び接地法により電気的クロストークも処理されるはずである。

#### 【0090】

図13b及び13cは、図13aに示される構成上で行われた実験の結果を示す。図13bは、チャネル1及びチャネル2の検出器D<sub>1</sub>及びD<sub>2</sub>からのオシロスコープトレースを示す。図13bは、光遅延発生器ODG<sub>E</sub>の周期内において2本のチャネルが若干異なる位置に配されていること、すなわち、相異なる深度における画像化をシミュレートするために試料アームミラーS<sub>1</sub>及びS<sub>2</sub>を少量だけ計画的にオフセットさせたことを反映する、光遅延発生器ODG<sub>E</sub>の周期内に相異なる点において、干渉縞が生じていることを示す。図13bは、それぞれのチャネルに強い画像化信号があり、いかなるクロストークの形跡もないことを示す。矢印232及び234は、組織試料の2つの相異なる点に相当させ得る、2つの相異なる試料からの反射を示す。さらに、それぞれの検出パルスのエンベロープの半値幅は光源L<sub>E</sub>のコヒーレンス長に相当しており、このことはそれぞれのチャネルの光信号が光源L<sub>E</sub>から発したことを示す。図13cは、試料点の内の方を他方の試料点に対して移動させた場合の実験結果を示す。この場合にも、クロストークは観測されなかった。

#### 【0091】

本発明の別の実施形態においては、多チャネルOCT法を診療に用い得るように、本明細書で先に開示された光ファイバネットワークが内視鏡に組み込まれる。本装置のファイバ束チップ12の大きさのため、ファイバ束チップ12は、(大径の治療用内視鏡には組み込み得るが)従来の診断用内視鏡の作業チャネルには適合しないであろう。したがって、別の設計手法がとられた。ファイバ束チップ12を従来の診断用内視鏡の作業チャネルに収容するように設計する代わりに、従来の診断用内視鏡の機能の全てをファイバ束チップ12の周りに配するように設計した。図14に示されるように、本発明の内視顕微鏡を組み込んでいる(図6のチップ56に相当する)GI内視鏡300の一実施形態は、直径がほぼ11mmである。これは、直径が8~9mmの従来の診断用内視鏡より若干大きい。GI内視鏡300は、従来の前面観察白色光画像化に加えて、上で開示された内視顕微鏡撮像能力を有する。したがって、GI内視鏡300の使用者は図16に示されるような2mm×2mm断層画像を得ることができるはずである。

#### 【0092】

GI内視鏡300は2.7mm径の吸引/生検チャネル302を備える。吸引/生検チャネル302の末端は、注目する組織領域306に向けられた開口304を提供するように曲げられる。吸引/生検チャネル302の軸は、注目する組織領域306の中心から約6.7mmにおくことができる。2本のチャネル308及び310が白色光照明のために設けられ、チャネル312が白色光内視鏡前面観察のために設けられる。チャネル308, 310及び312のそれぞれの直径は、2.7mmとすることができる。空気または水ノズルのための細チャネル314も設けられる。

#### 【0093】

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本発明にしたがえば、断層観察内視鏡コヒーレント光顕微鏡（E C O M）316がG I内視鏡300に設けられる。断層観察E C O M 316は（図14及び15には示されていない）ミラー16を回転させるための駆動機構318を備える。先に述べたように、動径、並進またはヘリカル走査を用いることができる。さらに、先に述べたように、機械的駆動機構の代わりにM E M S駆動機構を用いることができる。断層観察E C O M 316は、境界320で設定される深度及び境界322で設定される角度範囲を有する、注目する組織領域306にわたって走査するように構成される。さらに、光透過窓324を断層観察E C O M 316に設けることができる（図15参照）。

#### 【0094】

前面観察白色光チャネル312は30フレーム／秒のレートで更新される。断層観察E C O M 316で得られる断層画像は4.4フレーム／秒で更新される。全ての画像チャネルが同時に表示される。G I内視鏡300で生成され得る画像が図16及び17に示される。図16は、断層観察E C O M 316で達成できることが期待される空間分解能を組み入れた、ヒトの結腸上皮のシミュレーション画像である。図17a及び17bは、顕微鏡像と生体内O C T画像との比較である。図17aには、それぞれがヒトの皮膚の汗腺管の顕微鏡像を示す、2枚の写真がある。図17bには、それぞれがヒトの皮膚の汗腺管の生体内O C T画像を示す、3枚の写真がある。生体内O C T画像は波長1300nmで動作する光源により生成した。

#### 【0095】

内視鏡医によるG I内視鏡300の典型的な操作または使用には、以下の：

a) 一般的な内視鏡法の手順に続いて、従来の前面観察白色光チャネル312の案内の下にG I内視鏡300が挿入されるステップ；この操作は現時点で利用できるG I内視鏡の操作と異なることはないはずである；

b) 内視鏡医が顕微鏡検査を行う必要がある場合、彼／彼女がG I内視鏡300を押し込んで図13に示されるように内腔壁に接触させるステップ；光学系は、G I内視鏡300が組織に接触しているときに、光学系全体の正しい作動距離が得られるように設計される；G I内視鏡300は壁に接触しているが、図15に示されるように、顕微鏡検査下にある組織部分は接触しない；したがって、組織の表面構造が接触圧で変形することはない；しかし、このことはG I内視鏡300が接触モードでのみ動作し得ることを意味しない；実際上、G I内視鏡300は、画像が形成される限り非接触モードで動作することができ、これは先に述べた動的トリガ印加アルゴリズムが空気-組織界面を見いだすか否かにより規定される；空気-組織界面がシステムの作動距離内にあれば、先に‘適応トリガ印加’法で説明したように、検出された光パターンに界面が明瞭なピークを生じさせるから、界面は明確かつ容易に検出されるはずである；

c) 内視鏡医がステップ（b）で画像化した領域に隣接する領域を検査する必要があれば、内視鏡医がG I内視鏡300をひねり、視野を回転させて新しい位置におくことができるステップ；

が取り入れられるであろう。

#### 【0096】

胃腸（G I）管の映像化のための使用に現時点で最良の手法には、内視鏡超音波検査法（E U S）及び拡大内視鏡（M E）がある。ほぼ70から100mmの高周波E U Sの分解能は、組織の微細構造を擾乱する状況の多くの識別、とりわけG I管の浅層（粘膜及び粘膜下組織）内に生じる潜行性病理変化の識別には不十分である。倍率が×170までのM Eは微細な浅層粘膜パターンの優れた画像を提供するが、表面下構造及び病変期分類は決定できない。したがって、組織生検及び組織学が、現時点でも依然としてG I管に関わる顕微的疾患の検出のための医療標準である。

#### 【0097】

本明細書に開示された断層観察E C O M 316によれば、軸次元及び横断（横）次元のいずれにおいても5μmの分解能でG I壁の実時間2mm深度断層画像を得ることができる。参考のために、胃腸上皮細胞の大きさは平均して7から10μmであり、これは異形成

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または新形成変化がおこるにつれてさらに増大する。G I 管においては、2 mm の視深度であっても、粘膜起因疾患及びいかなる下層粘膜下組織への新形成浸潤のいずれの検出にも十分であり、このことは予後判定及び治療のために重要である。断層観察 E C O M 3 1 6 の画像分解能は、×100（総倍率）顕微鏡の下での無染色組織検査スライド観察に相当し得る。したがって、異形成（細胞性新形成変化）のような重要なエンティティーの多くあるいは粘膜固有層または粘膜筋板のような構造の新形成浸潤を、断層観察 E C O M 3 1 6 により識別可能とすることができます。

## 【0098】

本発明により、多様な顕微的粘膜病理及び病変期分類のその場診断が可能になり得る。基本的に、本“光生検”法は、標準的な生検及び組織学の方法の代わりになるか、最小限でも、手引きになり得る。これは、不必要的生検試料及び組織処理を減らし、患者のリスクを小さくし、サンプリングレート及び診判定率を高めて即時の診断フィードバックを医師にも患者にも提供し、（ある場合にはそれ自体が治療処置になり得る）生検を目標とすると言い直すことができる。少数の例を挙げれば、バレット食道、慢性潰瘍性大腸炎、初期扁平腺腫、または迷走結腸窩の病巣のような、前新形成 G I 状況には、断層観察 E C O M 3 1 6 が適用可能であり得る。現時点では、上記状況内での新形成進行の検出及びサーベイランスは、それらの顕微的性質により、最善とは言えない。

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## 【0099】

第2に、断層観察 E C O M 3 1 6 は、新形成及び非新形成の組織変化を時間を追って監視することを可能にする、機能性画像化システムとして役立ち得る。例えば、小さな腸絨毛の構造の回復及び炎症性細胞の減少を、グルテン過敏腸症、熱帯性スブルー及び腸インフェステーションのような、多様な腸の吸収不良性障害において、断層観察 E C O M 3 1 6 で監視できる。顕微レベルにおける多くの粘膜疾患の自然発達も、侵襲性を最小限に抑えた態様で評価できる。時間とともに生体内で進行している構造的細胞変化を監視できる能力は、細胞機能に関する重要な生理学的情報及び細胞の病理学的トランスマーチョンに関する洞察を提供できる。

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## 【0100】

第3に、断層観察 E C O M 3 1 6 は予後治療組織監視に使用できる。ガン切除の外科切除限界またはその予後治療サーベイランス中の処置限界または粘膜の前新形成状況の光力学治療の妥当性の評価の、生体内顕微的標定は、いくつかの例に過ぎない。

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## 【0101】

他の医学専門分野における応用も可能である。皮膚科学、血液学、（薬物及び放射線）腫瘍学、眼科学、泌尿器科学、外科学、呼吸器科学及び胃腸病学のような非常に多くの医学専門分野に、本明細書に開示された多チャネル OCT 装置が応用され得ることは、当業者には当然である。

## 【0102】

本明細書に開示された多チャネル OCT 装置は、システム性能をさらに向上させるために改変することができる。例えば、なされ得る改善には、光源から発せられる光に対するコード化伝送の採用があろう。この手法により、S N R が劣悪なチャネルで得られる干渉パターンの光の S N R を高めることで、画像分解能を高めることができる。

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## 【0103】

本明細書に説明され図示された好ましい実施形態に、本発明を逸脱することなく様々な改変がなされ得ることは当然であり、本発明の範囲は特許請求の範囲で定められる。例えば、本明細書に開示された構成図のそれぞれにおいて、3 d B 結合器の代わりに他の光結合器を用いることもできる。

## 【図面の簡単な説明】

## 【図 1 a】

光路を示し、空気 - 組織界面の反射効果を無視する、本発明にしたがう装置のチップの平面図である

## 【図 1 b】

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光路を示し、空気 - 組織界面の反射効果を無視する、本発明にしたがう装置のチップの側面図である

【図 1 c】

光路を示し、空気 - 組織界面の反射効果を無視する、本発明にしたがう装置のチップの端面図である

【図 1 d】

光路を示し、空気 - 組織界面の反射効果を無視する、図 1 a の装置のチップの別の実施形態である

【図 2 a】

図 1 のファイバ束チップを示す

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【図 2 b】

ファイバ束チップの拡大平断面図である

【図 2 c】

ファイバ束チップの端面の拡大断面図である

【図 3 a】

図 1 のファイバ束チップの撮像ファイバの内の 3 本の焦点を示す

【図 3 b】

相異なる深度にある焦点の詳細を示す図 3 a の焦点の拡大図である

【図 4 a】

図 1 のファイバ束チップから光ビームを向ける様々な方向を示す略図である

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【図 4 b】

図 4 a の方向 A 及び C における光ビームの平面図である

【図 4 c】

図 4 a の方向 A 及び C における光ビームの端面図である

【図 4 d】

図 4 a の方向 B 及び D に向けられる光ビームの平面図である

【図 4 e】

図 4 a の方向 B 及び D に向けられる光ビームの側面図である

【図 4 f】

方向 B 及び D における光ビームの斜視図を示す

30

【図 5 a】

多焦点域近傍の電場強度分布を示す、5 チャネルファイバ束チップのビームスポット図である

【図 5 b】

多焦点域近傍の電場強度分布を示す、15 チャネルファイバ束チップの中央 5 チャネルのビームスポット図である

【図 5 c】

図 5 a のファイバ束チップのビームスポット径対焦点域距離のグラフである

【図 5 d】

図 5 b のファイバ束チップのビームスポット径対焦点域距離のグラフである

【図 6】

本発明にしたがう装置の簡略なレイアウトである

【図 7 a】

本発明の装置に用いられる光遅延発生器の平面図である

【図 7 b】

図 7 a の光遅延発生器に用いられる走査ミラーの前面図である

【図 8 a】

ミラー及び図 1 a のファイバ束チップの内の 3 本の撮像ファイバからの焦点の端面図である

【図 8 b】

50

本発明の撮像ファイバの1本から放射された光に対する、結合された、A - 走査及び2次元輝度モード（B - モード）走査の経路を示す

【図9】

本発明の単一撮像ファイバの1本から放射されている光に対する、空気 - 組織界面による、コヒーレンスゲートと焦点との間の不一致を示す図である

【図10】

図9に示される不一致を解消させるための、本発明の装置の適応トリガ印加を示す図である

【図11a】

従来技術の单チャネル光コヒーレンス断層撮影装置の略図である

10

【図11b】

2チャネル光コヒーレンス断層撮影装置の略図である

【図11c】

Nチャネル光コヒーレンス断層撮影装置を構成するために用いられ得る光ネットワークの略図である

【図12a】

光サーチュレータをもつ单チャネル光コヒーレンス断層撮影装置の略図である

【図12b】

光サーチュレータを採用する2チャネル光コヒーレンス断層撮影装置の略図である

【図12c】

光サーチュレータを採用するNチャネル光コヒーレンス断層撮影装置を構成するために用いられ得る光ネットワークの略図である

20

【図13a】

光チャネル共有コンポーネント間のクロストークを調べるために用いられた実験装置構成の略図である

【図13b】

図13aの構成で実施した実験による実験結果である

【図13c】

図13aの構成で実施した実験による別の実験結果である

【図14】

30

本発明にしたがうG I内視鏡コヒーレント光顕微鏡の端面図である

【図15】

生検チャネルを示す図14のG I内視鏡コヒーレント光顕微鏡の破断側面図である

【図16】

本発明の装置により得られると考えられるヒトの結腸上皮のシミュレーション画像である

【図17a】

それぞれが人の皮膚の汗腺管の顕微鏡像を示す2枚の写真を示す

【図17b】

それぞれが人の皮膚の汗腺管の生体内O C T像を示す3枚の写真を示す

【符号の説明】

40

1 0 多束単一モードファイバ

1 2 ファイバ束チップ

1 4 集束レンズ

1 6 ミラー

1 8 表面

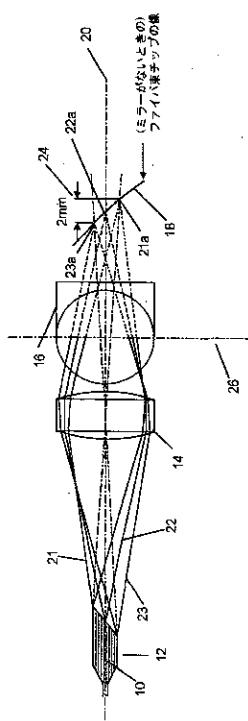
2 0 軸

2 1 , 2 2 , 2 3 ビーム

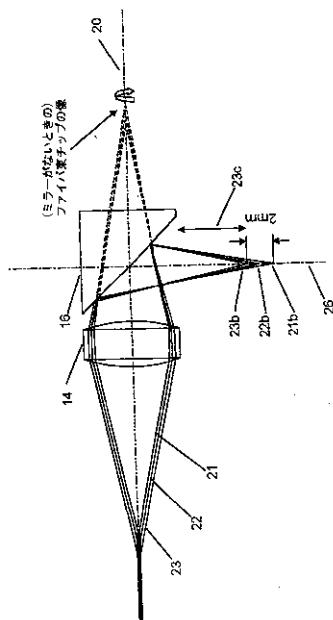
2 1 a , 2 2 a , 2 3 a 集束点

2 4 画像化深度

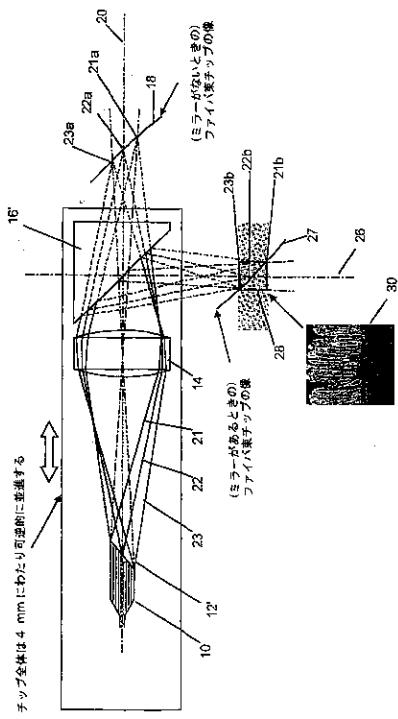
【図 1 a】



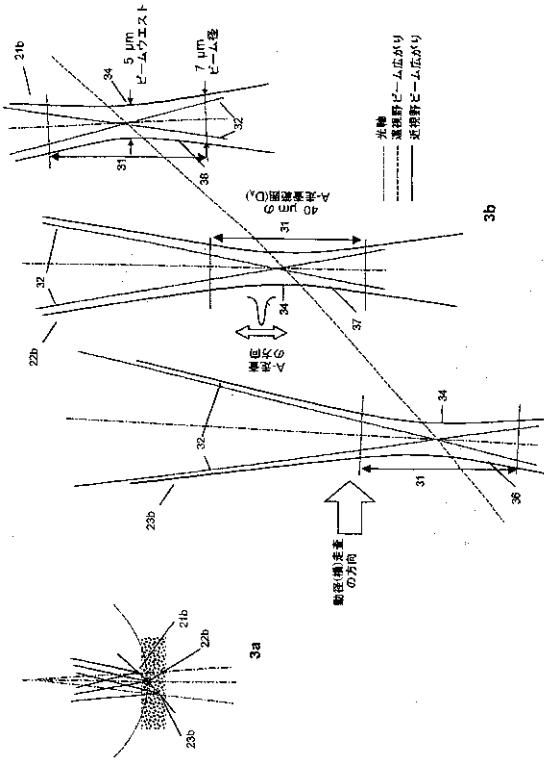
【図 1 b】



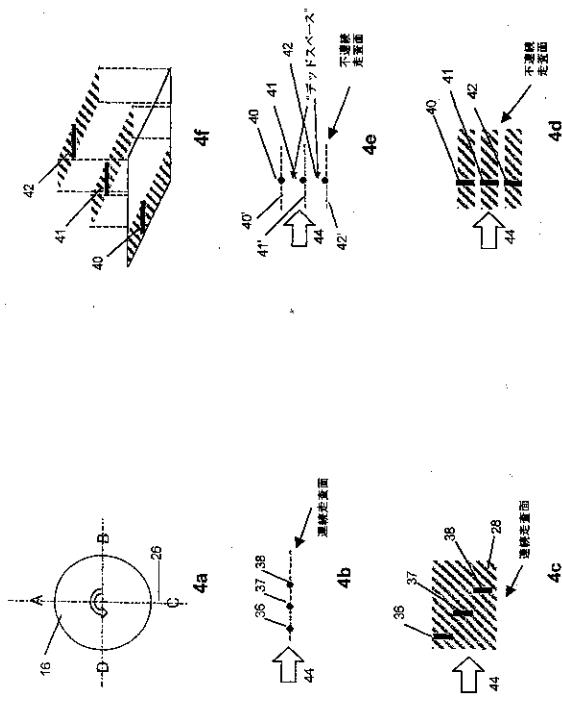
【図 1 d】



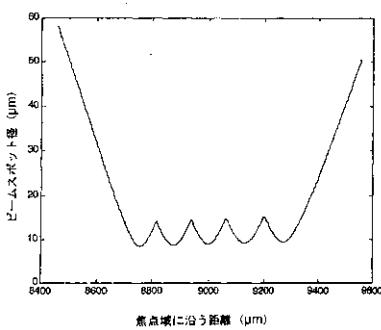
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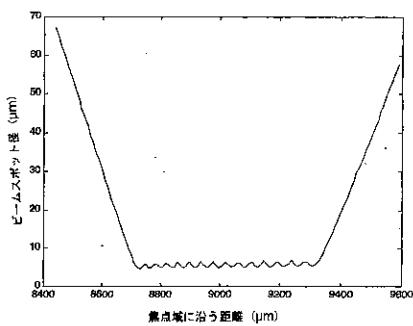
【図4】



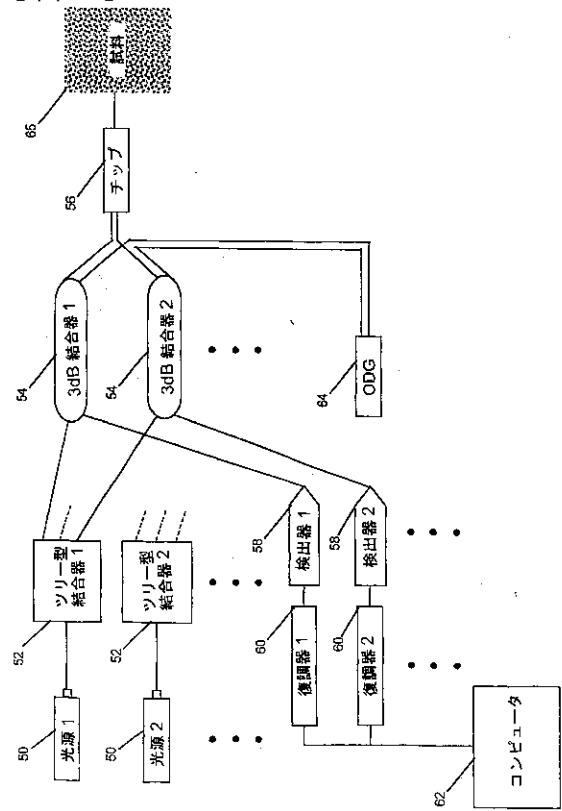
【図5 c】



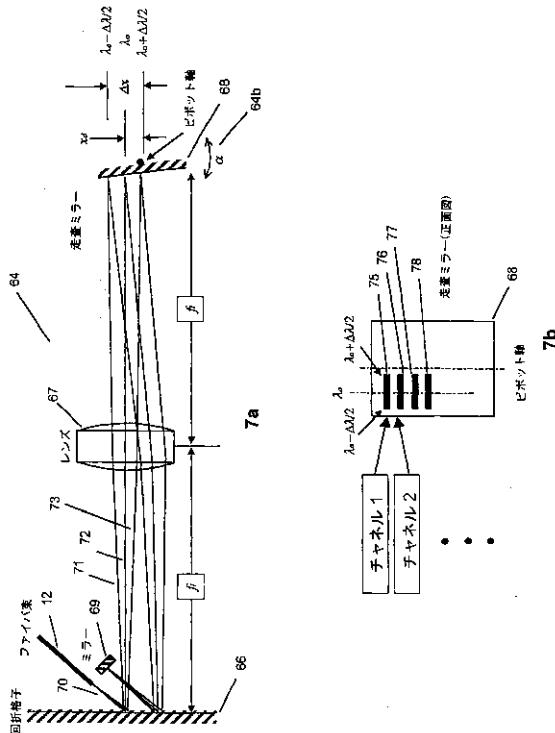
【図5 d】



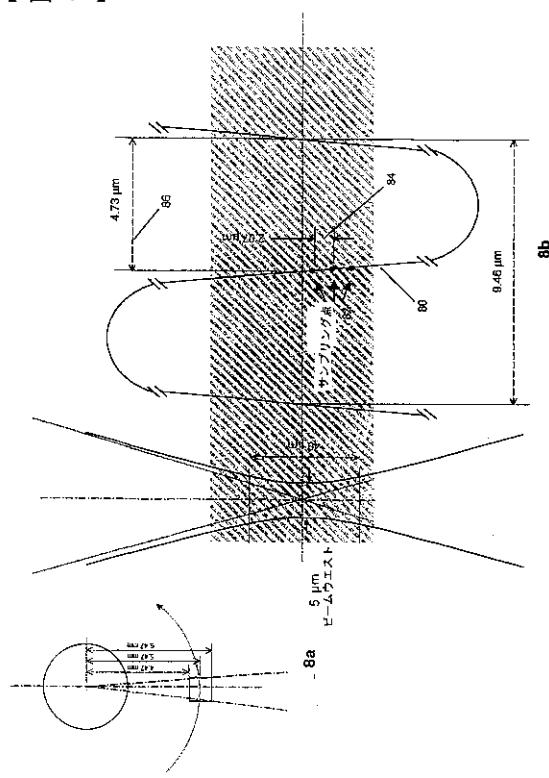
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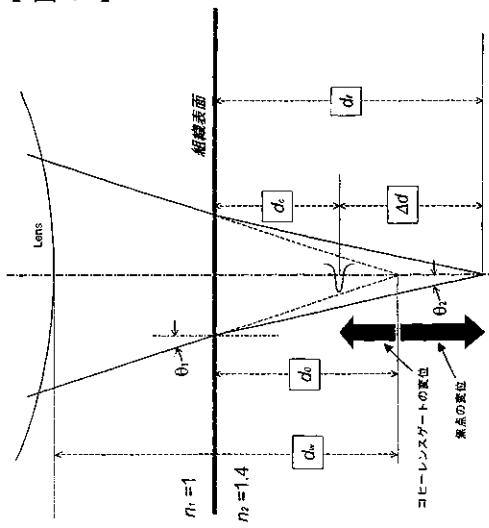
【図7】



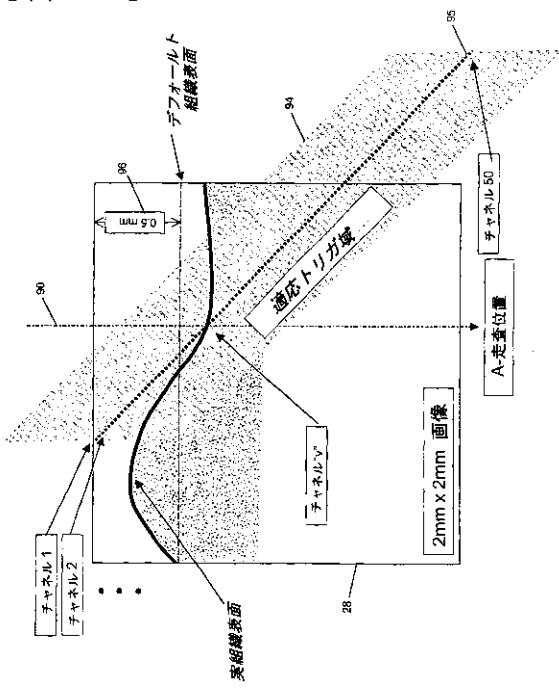
【図 8】



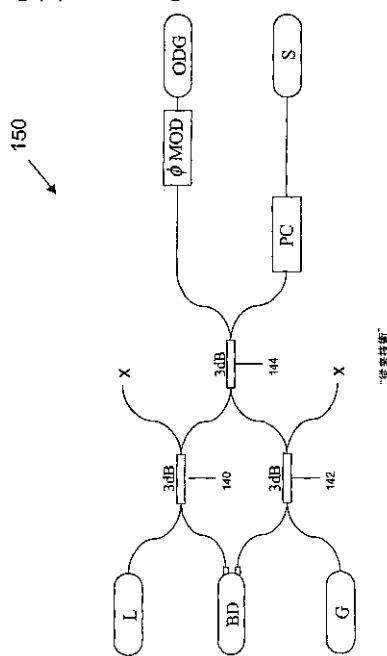
【図 9】



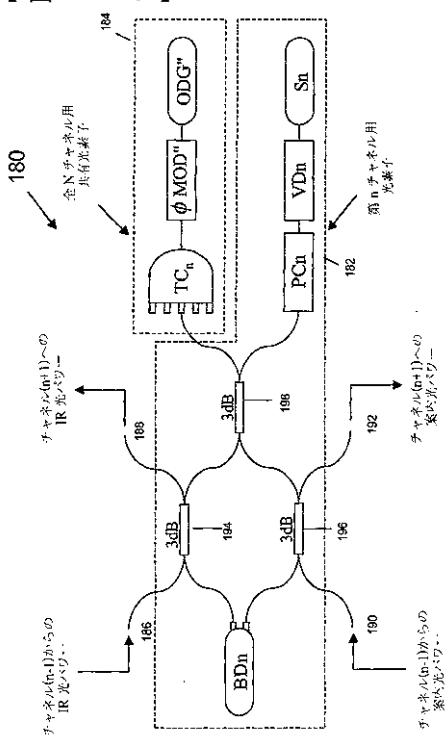
【図 10】



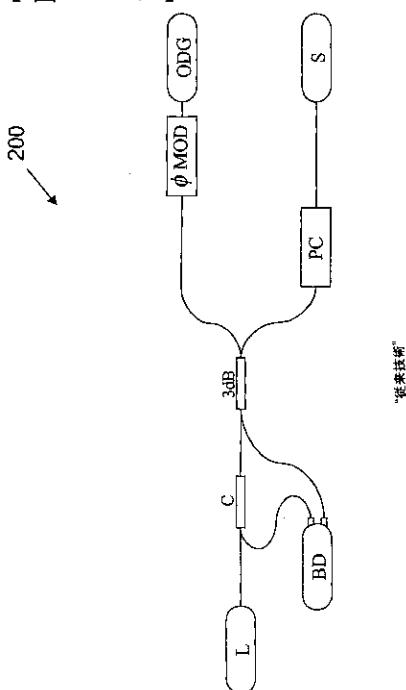
【図 11 a】



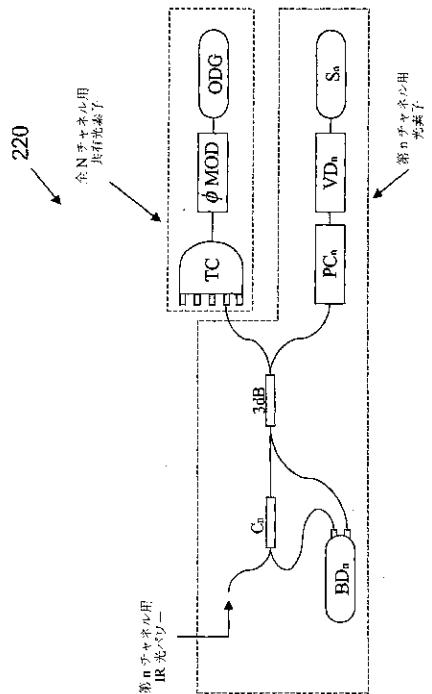
【図 1 1 c】



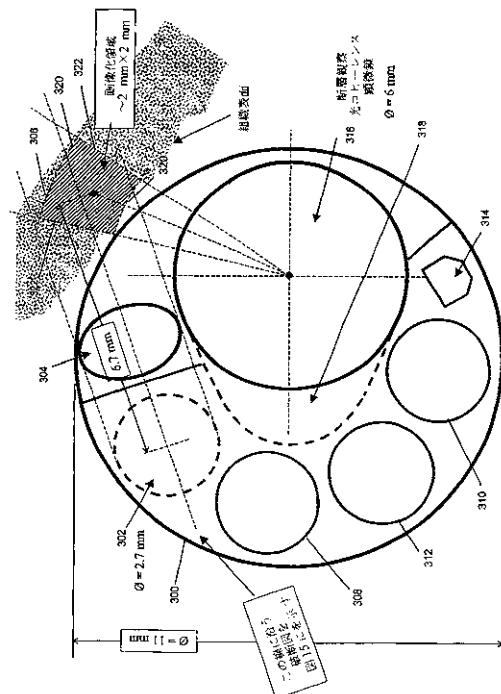
【図 1 2 a】



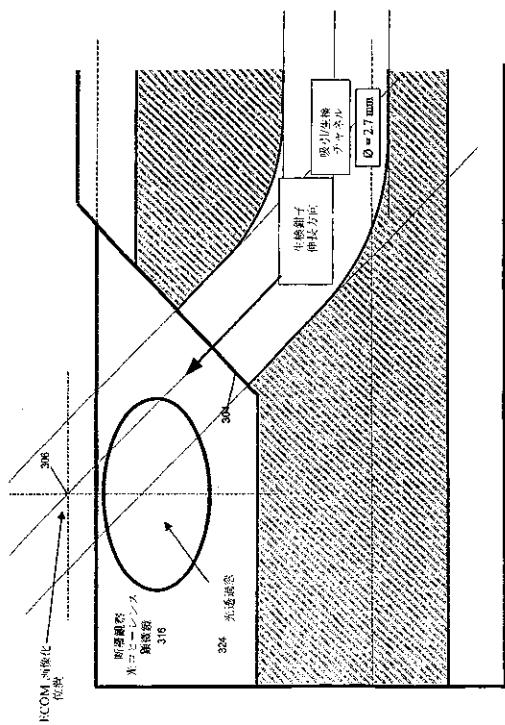
【図 1 2 c】



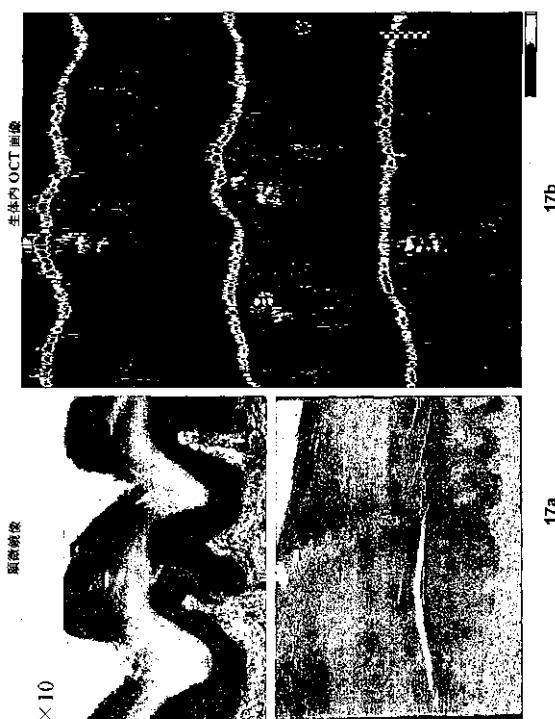
【図 1 4】



【図15】



【図17】



## 【国際公開パンフレット】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number  
WO 02/04929 A2(51) International Patent Classification<sup>7</sup>: G01N 21/47

Grove, Toronto, Ontario M6R 2Y6 (CA); MOK, Alvin,

(21) International Application Number: PCT/CA01/06992

Ho, Kwan (CA/CA), 187 Spadina Road, Richmond Hill,

(22) International Filing Date: 10 July 2001 (10.07.2001)

Ontario L1B 3C5 (CA).

(25) Filing Language:

English

(74) Agent: BERESKIN &amp; PARR, 40th Floor, 40 King Street

(26) Publication Language:

English

West, Toronto, Ontario M5H 3Y2 (CA).

(30) Priority Data:

60/217,990 16 July 2000 (10.07.2000) US

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LZ, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SL, TJ, TM, TR, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (for all designated States except US): UNIVERSITY HEALTH NETWORK (CA/CA); Room 7-504, 610 University Avenue, Toronto, Ontario M2G 2M9 (CA).

(84) Designated States (regional): ARTHO patent (GL, GR, KL, LS, MW, MZ, SD, SL, SZ, TZ, CG, ZW). European patent (AM, AZ, BY, KG, KZ, MD, RU, TL, TM). European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IL, LU, MC, NL, PT, SE, TR). OAPI patent (BJ, DJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors and

(75) Inventors/Applicants (for US only): YANG, Victor, Xiao, Dong (CA/CA), Unit 1-936B, 60 University Street, Toronto, Ontario M5S 3L1 (CA); VITKIN, I., Alex (CA/CA), 120 Glendale Avenue, Toronto, Ontario M6G 1R5 (CA); WONGKEESONG, Luuic (CA/US), Apartment 502, 211 2nd Street N.W., Rochester, MN 55901 (US); KATZ, Shmuel (IL/CA); 77 Winnipeg Avenue, Toronto, Ontario M4M 2X2 (CA); GORDON, Margaret, Leslie (CA/CA), 61 Dalwood Road, Toronto, Ontario M1P 2N4 (CA); WILLSON, Brian, C. (GB/CA); 85 Belmont

Published:  
— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

WO 02/04929 A2

(54) Title: METHOD AND APPARATUS FOR HIGH RESOLUTION COHERENT OPTICAL IMAGING

(57) Abstract: A method and an apparatus for examining the sub-surface microstructure of a sample are provided. Radiation from a plurality of optical radiation sources travels along a first optical path. In the first optical path, a device focuses the optical radiation from each of the optical sources into a plurality of respective focal points along the first optical path to provide substantially continuous coverage of a selected portion of the first optical path. Then, a sample on the first optical path within the selected length extending into the sample is scanned along said selected portion of the first optical path.

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**Title: METHOD AND APPARATUS FOR HIGH RESOLUTION COHERENT OPTICAL IMAGING**

**FIELD OF THE INVENTION**

5 This invention relates to both a method and an apparatus for high-resolution optical imaging. More particularly, this invention is concerned with providing high-resolution imaging suitable for incorporation into an endoscope.

**BACKGROUND OF THE INVENTION**

10 Modern medical imaging techniques have important applications in health care. Modalities such as X-ray computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound imaging are the main tomographic techniques available in most modern medical centers. Visible-light endoscopy is another major imaging modality which is used extensively in procedures like bronchoscopy or colonoscopy. Each of these techniques employs different physical principles and measures different properties of the biological tissue under study with different resolution. Further, they can commonly be performed *in-vivo*. A third type of imaging, 15 optical microscopy, is still utilized widely in clinical medicine. However, optical microscopy is currently limited to detailed examination of excised or resected specimens and is not used *in-vivo*. In many circumstances, the superior contrast and resolution afforded by optical microscopy is such that physical biopsy followed by optical microscopic histology is considered the 20 gold standard for diagnosis.

25 , Combinations of these techniques, such as using a low-resolution tomographic modality along with high-resolution imaging, biopsies or interventional procedures are constantly being studied and evaluated. Evaluation of these techniques is based on technological feasibility, clinical benefit and cost.

30 Optical Coherence Tomography (OCT) is a relatively new imaging technique based on the low-coherence property of electromagnetic radiation that enables high-resolution depth profilometry in a turbid, highly scattering

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media such as biological tissue. Its use in biomedical imaging is currently being investigated in several research and industrial laboratories. The main advantage of OCT lies in its ability to localize the depth of reflection from a sub-surface site in tissue. This localization is essentially determined by the 5 coherence properties of the light source used and can be as low as 2 to 20  $\mu\text{m}$  for selected near-IR sources (e.g. lasers or amplified spontaneous emission devices). This gives a measure of the depth resolution attainable with OCT. Independently of the coherence characteristics, the lateral resolution is determined by the beam cross-section at the depth of imaging 10 and by the lateral spacing of the acquired data. Typical values for lateral spacing in the literature are in the 5 to 30  $\mu\text{m}$  range. The price to be paid for this remarkable cross-sectional imaging ability in intact turbid tissue is the limited imaging depth since, due to multiple scattering and absorption, both coherence and penetration of light are degraded resulting in OCT imaging 15 depths of approximately 2 to 3 mm.

Most current implementations of OCT are based on Michelson interferometry with a 50/50 beam splitter directing the incident coherent light beam into a reference path containing a mirror (i.e. a reference arm) and a sample path containing the interrogated sample (i.e. a sample arm). Both 20 free-space optic and fiber-optic implementations of this scheme are currently used. Reflected beams from the mirror in the reference arm and from the tissue in the sample arm are recombined in the same splitter and half of the resultant light energy impinges on a detector. Incoherent superposition of the two light fluxes typically occurs except when the optical path lengths of the 25 two beams are matched to within the coherence length of the source. Within this limited distance, the coherent superposition of the two light fluxes yields an interference pattern with a fringe magnitude that is proportional to the reflectivity of the tissue at that particular depth. Depth profiling of the sample is then achieved by scanning the reference arm length or more correctly by 30 scanning the optical path length of the reference arm by using a time delay in the reference arm (this is equivalent to lengthening the reference arm). Various detection methods to measure and quantify these faint amplitude

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modulations amidst large background diffuse reflectance have been developed having a dynamic range of approximately 70 to 110 dB. Furthermore, lateral translation of the beam and axial motion of the reference mirror enables one to construct a two-dimensional reflectivity picture over a desired field of view. Means of improving the final image quality, such as performing image processing through de-convolution, have also been investigated.

The foregoing is a brief description of conventional reflectivity OCT imaging. Other variations include, for example, flow (Doppler) imaging and polarization imaging (albeit at the expense of additional complexity of the OCT optics and/or signal processing techniques). Images from these additional techniques are usually obtained in conjunction with images from conventional OCT so some image overlay or fusion is possible. Upon further technological development and/or clinical implementation, may add sufficient information content to increase the clinical utility of OCT in medicine.

However, many OCT designs and approaches that have been successfully implemented in tabletop research systems are not directly suitable for *in-vivo* imaging such as in gastroenterologic or bronchoscopic endoscopy. Instead, they may be more suitable for dermatological, ophthalmologic and dental applications. In contrast, *in-vivo* OCT imaging must address the issues of speed, resolution, contrast, penetration and instrument size. Images must be obtained sufficiently quickly to negate the effects of patient motion while still achieving suitable axial and lateral resolution, and maintaining an instrument size which is small enough to be endoscopically useful. Powerful near-IR sources, fast means of altering the reference arm length and custom-designed distal optical devices have been successfully developed to overcome the difficult challenges posed by *in-vivo* endoscopy.

The latest OCT technology employs a single-mode optical fiber with distal side-viewing optics introduced into the accessory channel of a conventional white-light endoscope. To build-up an image, the viewing direction of the OCT fiber is either linearly scanned to and fro over an approximate 2 mm distance, or is rotated via a flexible guide-wire or

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interlocking gear mechanism at several revolutions per second. Simultaneous with this translation or rotation, the reference arm length outside the endoscope is rapidly varied via an optical phase delay to generate depth scans (i.e. A-scans). Currently, these OCT systems operate 5 at frame rates up to conventional video rates but more typically at 4 to 8 frames per second, with a frame presenting a fully circumferential view to a depth of 2 to 3 mm. The resultant resolution values are approximately 5 to 25  $\mu\text{m}$  in the depth (axial) direction and approximately 20 to 40  $\mu\text{m}$  in the lateral direction. As well, the lateral resolution generally degrades with an 10 increase in distance from the fiber tip of the OCT device due to geometric divergence. These OCT systems have a dynamic range which is somewhat lower than that of corresponding ex-vivo systems due to increased noise levels and faster imaging speeds.

Based on the latest OCT technology, it is questionable whether 15 coherent *in-vivo* OCT systems are adequate for successful clinical imaging. The images are certainly useful, but substantial improvement is required if the elusive goal of "optical biopsy" is to be realized. For example axial and lateral resolution can be improved. While the improvement in the former usually involves the use of better low-coherence sources (i.e. CW and 20 pulsed sources), the issue of sub-optimal and depth-varying lateral resolution is more difficult to address. In ex-vivo systems, with its relaxed constraints of speed and physical size, lateral resolution is improved by focusing the beam to a few microns with a high-NA (numerical aperture) objective lens. In contrast to conventional OCT scanning, the imaging can 25 now be performed in the lateral (*en face*) direction with a pre-selected depth with small oscillations in path length difference, followed by a small depth increment as necessary. The high-NA objective lens is often coupled to tissue via a refractive-index matching liquid. The general approach of using OCT with a high-NA distal optic lens is known as Optical Coherence 30 Microscopy (OCM). However, the improved lateral resolution at the beam waist location comes at the expense of lateral blurring at other depths because the highly focused beam has a very shallow depth of field. Thus,

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the lens-to-surface distance must be varied to focus to different depths. In addition, a dynamic tracking scheme is needed to keep the location of the coherence gate (within which coherent interference between the optical beams from the sample arm and the reference arm is possible) and the beam waist at the same depth. These techniques for lateral resolution improvement have not been attempted during *in-vivo* endoscopy because of size and speed requirements.

#### **SUMMARY OF THE INVENTION**

10 The present invention is based on the concept of providing an endoscopic optical coherence tomography (OCT) device with microscopic resolution which will hereinafter be referred to as an endomicroscope. After reviewing possible clinical applications of the endomicroscope, the following parameters and features were identified since it is difficult to achieve these 15 parameters and features simultaneously with current *in vivo* OCT systems.

##### **1. High Resolution**

20 In order to achieve cellular and sub-cellular resolution, an endomicroscope should preferably resolve features smaller than 5  $\mu\text{m}$  both in the axial and lateral directions. In contrast to most existing *in vivo* OCT systems, the lateral resolution must not degrade substantially with the depth 25 of the tissue being imaged due to geometric divergence.

##### **2. Large field of view**

25 An appropriate field of view of the endomicroscope is approximately  $2 \times 2$  mm in the axial and lateral directions of the optical axis. This field of view is considered to be adequate for clinical applications. In order to achieve a 5  $\mu\text{m}$  resolution in both the axial and lateral directions throughout the entire image, more than 800 A-scans (i.e. depth scans) have 30 to be performed for each frame. The resultant image will contain more than 640,000 pixels. This is several orders of magnitude higher than existing *in vivo* OCT systems.

3. Small size of endoscope tip

Most of the existing *in vivo* OCT systems are designed around the constraints of the instrument channel of existing endoscopes. As a result, 5 the outer diameter of these systems is restricted to approximately 2 to 3 mm which limits the numerical aperture of the imaging system. This makes it difficult to obtain high lateral resolution under *in vivo* conditions. These constraints may be technically unnecessary and limit one from fully 10 exploiting the benefit of OCT/OCM in the clinical applications under consideration. Accordingly, a larger outer diameter, such as 3 mm or more, for example, may be used for the endoscope as well as a length of less than 20 mm for the rigid tip.

4. High imaging speed

15 Since the endomicroscope will be used to image a large area at high resolution under *in vivo* conditions, motion artifacts must be considered because of tissue motion due to physiological motion. These motion artifacts should be eliminated to ensure good image quality. Accordingly, the endomicroscope should preferably be able to acquire a single frame 20 image within 12.6 ms given a typical physiological motion speed of 5 mm/s. This results in 63,000 A-scans per second. This imaging speed is more than one order of magnitude higher than that of current *in vivo* OCT systems.

5. Integration with currently available endoscopic imaging procedures

25 In order to improve clinical usefulness, conventional white light imaging should preferably be integrated into the endomicroscope. In addition, instrument channels should be preferably designed so that an excisional biopsy could be performed under the guidance of the endomicroscope. As well, instrument channels for water and air delivery 30 may be preferably made available.

The advanced requirements for an endomicroscope outlined above are not compatible with existing OCT/OCM designs. For instance, if

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an outer diameter of 6 mm is allowed for the endomicroscope and a distal optical design is used based on a single rotating fiber as described by Tearney, G.J., Brezinski, M.E., Bouma, B.E., Boppart, S.A., Pitriss, C., Southern, J.F., and Fujimoto, J.G. ("In vivo Endoscopic Optical Biopsy with 5 Optical Coherence Tomography", *Science*, **276**: 2037-2039, 27 June 1997), then although the 5  $\mu\text{m}$  lateral resolution can be achieved at a single specific depth within the tissue in any one scan, such lateral resolution will degrade due to beam divergence at other depths. In addition, since a high 10 NA system will be required to produce the requisite small beam waist size, the coherence gate and the focal point will not stay together in depth over a substantial (e.g. 2 mm) distance unless some dynamic compensation is implemented as described by Schmitt, J.M., Lee, S.L., and Yung, K.M ("An 15 Optical Coherence Microscope with Enhanced Resolving Power in Thick Tissue", *Optics Communications*, **142**: 203-207, 1997). Therefore, in order to achieve some of the aforementioned requirements of the 20 endomicroscope, dynamic focusing (changing the probe/tissue distance) and dynamic compensation (changing the path length difference) must be used. However, these focusing and compensation techniques complicate the practical realization of the device and may make it more difficult to 25 satisfy the high imaging speed requirement. If one tries to first satisfy the imaging speed, as described by Rollins, A.M., Kulkarni, M.D., Yazdanfar, S., Ung-arunyawee, R., and Izatt, J.A. ("In vivo Video Rate Optical Coherence Tomography", *Optics Express*, Vol. 3 No. 6: 219-229, 14 September 1998), then image resolution, particularly lateral resolution, is degraded to an extent that the clinical utility of the device is compromised.

The present invention provides an endomicroscope with multiple fibers (i.e. channels) employing OCT to allow for different parts of the image to be scanned in parallel, instead of in series as is currently implemented in existing *in vivo* or *ex vivo* OCT/OCM systems. Using multiple parallel 30 channels focused to different depths in the tissue, with each channel collecting high-resolution OCT data only across a very small axial range allows for a series of tight focal points to be achieved throughout the entire

field of view without dynamic focusing or dynamic compensation. This greatly simplifies the design of the device which may now use mostly fixed optical components, and may facilitate high-speed operation. In addition, the intrinsically miniature dimension of the fiber optic based OCT technique 5 makes the multichannel concept possible to implement in a flexible endoscopic device while the proximal part of the endoscope, which is outside of the patient, allows room for sources, detectors, and other equipment.

In accordance with a first aspect of the present invention, there is 10 an apparatus for optical examination of a sample, the apparatus comprising:  
an optical source means for providing a plurality of separate  
optical radiation sources;  
a first optical path extending from the source means; and,  
a focusing means in the first optical path for focusing optical 15 radiation from the optical radiation sources into a plurality of respective focal points located on a surface within the first optical path to provide substantially continuous coverage of a selected portion of the first optical path, whereby, in use, a sample can be located at least partially within the selected portion, thereby permitting simultaneous scanning of a plurality of  
points within the sample.  
20

In accordance with a second aspect of the present invention, an N channel apparatus for optical examination of a sample, wherein the N channel apparatus comprises a plurality of optical networks and a reference arm, each optical network providing one channel for the N channel 25 apparatus and sharing the reference arm.

In accordance with another aspect of the present invention, there is provided a method for optical examination of a sample, the method comprising:

- (a) providing radiation from a plurality of separate optical 30 radiation sources, along a first optical path;
- (b) providing focusing means in the first optical path;
- (c) focusing the optical radiation from the optical sources into a plurality of respective focal points along a surface within the first optical

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path to provide substantially continuous coverage of a selected portion of the first optical path; and

(d) providing a sample located at least partially within the first optical path; and,

5 (e) simultaneously scanning a plurality of points within the sample.

It is to be appreciated that a sample, for use with the present invention, may comprise any biological tissue or other suitable material.

Further objects and advantages of the invention will appear from 10 the following description, taken together with the accompanying drawings.

**BRIEF DESCRIPTION OF THE DRAWINGS**

For a better understanding of the present invention and to demonstrate how it may be carried into effect, reference will now be made, 15 by way of example, to the accompanying drawings which show a preferred embodiment of the present invention and in which:

Figure 1a is a top view of the tip of an apparatus in accordance with the present invention showing optical paths and ignoring the refraction effects of an air-tissue interface;

20 Figure 1b is a side view of the tip of an apparatus in accordance with the present invention showing optical paths and ignoring the refraction effects of an air-tissue interface;

Figure 1c is an end view of the tip of an apparatus in accordance with the present invention showing optical paths and ignoring the refraction 25 effects of an air-tissue interface;

Figure 1d is an alternate embodiment of the tip of the apparatus of Figure 1a showing optical paths and ignoring the refraction effects of an air-tissue interface;

Figure 2a shows the fiber bundle tip of Figure 1;

30 Figure 2b is a top view of an enlarged section of the fiber bundle tip;

Figure 2c is an end view of an enlarged section of the fiber bundle tip;

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- Figure 3a illustrates the focal points of three of the imaging fibers of the fiber bundle tip of Figure 1;
- Figure 3b is a magnified view of the focal points of Figure 3a showing details of the focal points at different depths;
- 5 Figure 4a is a schematic indicating different directions for directing the optical beams from the fiber bundle tip of Figure 1;
- Figures 4b and 4c are top and end views of optical beams in directions A and C of Figure 4a;
- 10 Figures 4d and 4e are top and side views of optical beams directed in directions B and D of Figure 4a;
- Figure 4f shows a perspective view of the optical beams in the directions B and D;
- Figure 5a is a beam spot diagram of a 5 channel fiber bundle tip showing electric field strength distribution near multiple focal zones;
- 15 Figure 5b is a beam spot diagram of 5 central channels of a 15 channel fiber bundle tip showing electric field strength distribution near multiple focal zones;
- Figure 5c is a graph of beam spot diameter versus focal zone distance for the fiber bundle tip of Figure 5a;
- 20 Figure 5d is a graph of beam spot diameter versus focal zone distance for the fiber bundle tip of Figure 5b;
- Figure 6 is a schematic layout of an apparatus in accordance with the present invention;
- Figures 7a is a top view of an optical delay generator used in the 25 apparatus of the present invention;
- Figure 7b is a front view of a scanning mirror used in the optical delay generator of Figure 7a.
- Figure 8a is an end view of the mirror and the focal points from three of the imaging fibers of the fiber bundle tip of Figure 1a;
- 30 Figure 8b shows a combined A-scan and a two-dimensional brightness-mode (B-mode) scan path for light radiated from a single imaging fiber of the present invention;

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- Figure 9 is a diagram illustrating mismatch between the coherence gate and the focal point due to the air-tissue interface for light radiating from a single imaging fiber of the present invention;
- 5 Figure 10 is a diagram illustrating flexible triggering of the apparatus of the present invention to accommodate the mismatch shown in Figure 9;
- Figure 11a is a schematic diagram of a Prior Art single channel Optical Coherence Tomography device;
- 10 Figure 11b is a schematic diagram of a two channel Optical Coherence Tomography device;
- Figure 11c is a schematic diagram of an optical network that could be used to construct an N-channel Optical Coherence Tomography device;
- 15 Figure 12a is a schematic diagram of a single channel Optical Coherence Tomography device with an optical circulator;
- Figure 12b is a schematic diagram of a two channel Optical Coherence Tomography device employing optical circulators;
- 20 Figure 12c is a schematic diagram of an optical network that could be used to construct an N channel Optical Coherence Tomography device employing an optical circulator;
- Figure 13a is a schematic of an experimental setup used to investigate cross-talk between optical channels sharing components;
- 25 Figure 13b is an experimental result from experimentation on the setup of Figure 13a;
- Figure 13c is another experimental result from experimentation on the setup of Figure 13a;
- Figure 14 is an end view of a GI endoscopic coherent optical microscope in accordance with the present invention;
- 30 Figure 15 is a cutaway side view of the GI endoscopic coherent optical microscope of Figure 14 showing a biopsy channel;
- Figure 16 is a simulated image of a human colon epithelium that is expected to be obtained with the apparatus of the present invention;

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Figure 17a has two panels which each show a microscopy image of sweat ducts in the human skin; and,

Figure 17 b has three panels which each show an *in vivo* OCT image of sweat ducts in the human skin.

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#### DETAILED DESCRIPTION OF THE INVENTION

In the following description, various specific dimensions and other parameters are mentioned such as the wavelength used by the imaging source and the physical dimensions of the optical components used in the apparatus. It is to be appreciated that this is for exemplary purposes only and does not limit this invention. Specific parameters, dimensions and the like may be chosen depending on an intended application of the invention.

Referring to Figure 1, the present invention provides an apparatus comprising an endoscopic coherent optical microscope having multiple single mode fibers 10, a fiber bundle tip 12, a focusing lens 14 and a mirror 16. The multiple single mode fibers 10 and the focusing lens 14 are stationary while the mirror 16 is rotatable. Accordingly, the mirror 16 is mounted for rotation in known manner. Details of the rotating mechanism for the mirror 16 are not described further and can be conventional. Multiple single mode fibers 10 (of which there may be approximately 50 fibers) form an array at the fiber bundle tip 12. This array is cleaved and arranged in a "staircase" pattern as shown in Figure 2. Radiated light from the fiber bundle tip 12 is focused by the focusing lens 14 and reflected by the mirror 16. The focusing lens 14 may have a diameter of 5 mm (i.e.  $\phi = 5$  mm) and a focal length of 5 mm (i.e.  $f = 5$  mm). The mirror 16 may have a diameter of 5 mm and a front face that is cleaved at 45°. A magnified image of the focal points of the fiber bundle tip 12 is shown in Figure 3.

Figure 1a shows three beams 21, 22 and 23 from three exemplary fibers arbitrarily chosen from the multiple single mode fibers 10. Due to the staggered or staircase nature of the multiple single mode fibers 10 (see Figure 2), each of the beams 21, 22 and 23 originates from a different point and consequently is brought into focus, by the focusing lens

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14, at a different point 21a, 22a and 23a on a surface 18 when the mirror 16 is not used. It will be appreciated that a similar effect is achieved for all of  
- the multiple single mode fibers 10 of the fiber bundle tip 12 to produce  
5 beams focused to different points on the surface 18. As indicated at 24 (and  
as shown in Figure 3), if the multiple single mode fibers 10 comprise 50  
optical fibers, each being focused within a short range of approximately 40  
microns and having their ends staggered to space the focal points apart by  
40 microns (as measured along axis 20 of the focusing lens 14), a total  
range or depth of 2 mm is covered. The axis 20 for the focusing lens 14 is  
10 part of a first optical path.

With the mirror 16 present, the optical beams 21, 22 and 23 are focused as shown in Figures 1b and 1c. Thus, three focal points 21b, 22b and 23b are spaced apart in a vertical or depth direction along axis 26 which forms an extension of the first optical path. As the view of Figure 1c shows, the three focal points 21b, 22b and 23b are also spaced apart in the circumferential direction (i.e. they are spaced apart laterally) relative to the motion of the mirror 16. The three focal points 21b, 22b and 23b fall on a surface 27 to facilitate imaging of a selected portion of the first optical path. The surface 27 may be a complex surface or a planar surface. If multiple  
15 single mode fibers 10 comprises 50 individual fibers, then the focal points of all the individual fibers from the fiber bundle tip 12 would be spaced apart correspondingly. Alternatively, the reflected focal points 21b, 22b and 23b do not necessarily have to be perpendicular to the axis 20 but may be at a large angle to the axis 20.

20 Rotation of the mirror 16 results in motion of the surface 27. This enables a two-dimensional B-scan image 30 to be obtained, as shown in Figure 1c, covering a scan area 28 which has a square shape with preferable dimensions of 2 mm x 2 mm. The B-scan image 30 indicates an exemplary view that may be obtained for the scan area 28.

25 Redesigning the multiple single mode fibers 10, for example, by changing the diameter of the core and cladding of the multiple single mode fibers 10, results in variations on the surface 27. Furthermore, optical wave

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guide wafers may also be used in the place of the multiple single mode fibers 10.

In an alternative embodiment, the mirror 16 may be replaced by a mirror 16' that moves linearly in combination with the focusing lens 14 and the fiber bundle tip 12 as shown in Figure 1d. The linear translation may preferably incorporate a reciprocal motion. In terms of mechanics, the fiber bundle tip 12, depicted in Figure 1a, utilizes a radial scanning motion. The radial scanning motion is well suited for scanning organs having larger diameters, such as the esophagus or the large intestine. However, due to the complex driving mechanism needed for radial scanning, the diameter of the fiber bundle tip 12 will not allow for endomicroscopy in organs having small inner diameters such as blood vessels. Therefore, the alternative embodiment shown in Figure 1d may be used which comprises a similar fiber bundle tip 12' that is adapted to perform linear translational scanning instead of radial scanning.

As shown in Figure 1d, the main differences between the two methods of scanning are that the mirror 16' will not be rotating and the entire fiber bundle tip 12' needs to be translated along its horizontal axis in preferably a reciprocal motion over a range of 4 mm for example. Mechanically, the linear translational scanning motion is less complicated than the radial scanning motion. In addition, linear translational scanning is better suited for endomicroscopy in organs having a small inner diameter such as blood vessels. However, for some larger organs, such as the large intestine, linear translational scanning is not as well suited due to positioning difficulties.

In a further alternative embodiment, both of the scanning motions may be combined to produce an endomicroscopy device having helical scanning. The helical scanning motion would comprise the rotational movement of the mirror 16 in combination with the linear translation of the mirror 16, the focusing lens 14 and the fiber bundle tip 16. Such an endomicroscopy device may be more suitable for imaging certain types of organs such as the human large intestine. The helical scanning

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endomicroscopy device may be implemented by linearly translating the apparatus shown in Figure 1a.

In yet another alternative embodiment, the fiber bundle tip 12 may be altered to employ a Micromachined Electro-Mechanical System (MEMS) driving mechanism. Since the aforementioned embodiments require some form of motion for the mirror 16, all embodiments require mechanical driving mechanisms. Accordingly, a motor is situated outside of the endoscope and a mechanical drive-train mechanism or wire is placed along the entire length of the endoscope. However, the multi-channel fiber optical design is not restricted to such mechanical driving means. In fact, due to the extremely small spatial resolutions realizable by the multi-channel system, adverse effects, such as vibration induced polarization dependence, from the mechanical drive means, may limit the full potential of the present invention if a mechanical drive means is utilized. Therefore, a MEMS electrical driving mechanism may be employed where electrically-driven, micro-mechanical optical devices are used to facilitate the scanning. This implementation may potentially circumvent the adverse effects that may be caused by a mechanical driving mechanism since the MEMS implementation reduces vibrations along the axis of the device except in the vicinity of the object which is being translated such as the mirror 16. The MEMS implementation may also offer advantages in terms of miniaturization and performance.

In a further alternative embodiment, the fiber bundle tip may not require the mirror 16. The combination of the fiber bundle tip 12 and the focusing lens 14 may be pivotally attached. Accordingly, through a pivoting motion, the combination of the fiber bundle tip 12 and the focusing lens 14 may be adapted to direct a plurality of focusing points along portions of a plurality of surfaces extending into the sample to construct the B-scan image 30 of the scan area 28.

In yet another embodiment, the mirror 16 may be a surface of a prism. The rest of the apparatus would follow as previously described and shown in Figures 1a to 1d.

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It should further be understood that the optical path can be straight, bent or curved. Furthermore, the optical path may be a 3 dimensional path having a length, width and height. Depending on the scanning motion (i.e. radial, linear or helical), the orientation of the surface, 5 upon which the focal points reside, may also vary. Furthermore, the optical path may comprise optical radiation from one optical radiation source or a plurality of optical radiation sources (i.e. a plurality of light sources or a plurality of fibers each transmitting optical radiation).

Referring now to Figures 2b and 2c, a magnified view of the fiber 10 bundle tip 12 comprising the multiple single mode fibers 10 is shown. Each 10 of the multiple single mode fibers 10 comprises a cladding 10a around a core 10b having diameters of, for example, 40  $\mu\text{m}$  and 5  $\mu\text{m}$  respectively. The ends of the multiple single mode fibers 10 may be stepped by 40  $\mu\text{m}$  so 15 that the focal points of the optical radiation through each of these fibers are spaced apart. However, a step spacing other than 40  $\mu\text{m}$  may also be used.

Referring now to Figure 3, A-scans for each of the multiple single mode fibers 10, in the fiber bundle tip 12, are acquired over approximately 20 the entire 2 mm imaging depth, but retained only over a short axial range of approximately 40  $\mu\text{m}$  near the focal point of each fiber where the beam diameter is close to a minimum (indicated at 34) and does not vary substantially with axial position. This range of 40  $\mu\text{m}$ , in this exemplary design, is indicated at 31. The A-scans are performed simultaneously by 25 each of the multiple single mode fibers 10 within the fiber bundle tip 12. Effectively, the multiple A-scans cover the entire depth of 2 mm in the sample tissue at different radial directions, but for each of the multiple single mode fibers 10, only sections of the respective A-scan in a corresponding 30 40  $\mu\text{m}$  depth-of-focus 31 are used to build up the image. As shown in the focal zone 31, each of the beams 21b, 22b and 23b show a distinct "hourglass" shape for the focal points 38, 37 and 36, in known manner. For each of the beams 21b, 22b and 23b, the far field beam spread is indicated by lines 32 and the near field beam spread is indicated by lines 34.

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The purpose of rotating the mirror 16 is to create radial (i.e. lateral) scans in a direction that is perpendicular to the A-scan direction to create a B-scan image, i.e. the scan area 28 of Figure 1. The resultant radial scan pattern of the focal points of the individual fibers from the 5 multiple single mode fibers 10 is illustrated in Figure 4. It is worth noting that a continuous scan surface is only present when the cleaved face of the mirror 16 is faced substantially in the direction of locations "A" and "C", where B-scan images should be taken. At other locations on the radial scan 10 pattern, a "dead space" between the individual A-scans is too large to allow for sufficient sampling of the tissue. Therefore, the present invention 15 comprises a sector-scan imaging device, to scan a sector substantially in the "A" or "C" locations, with a sector angle of about 20°, within which a 2 mm by 2 mm image is obtained. In this example, with the given geometry, a larger sector angle will produce "dead spaces" which are too large to form a suitable cross-sectional image.

Figures 4b and 4c show beam focal points 36, 37 and 38 from both a top view and an end view respectively. As shown, and corresponding to earlier figures, the individual focal points 36, 37 and 38 are spaced apart 20 in the radial plane perpendicular to the axis 20. As Figure 4c shows, in an end view along the axis 26, the focal points 36, 37 and 38 are spaced apart in terms of depth but overlap to create a continuous scanning surface or 25 scan area 28.

If, the cleaved face of the mirror 16 is faced substantially in the direction of the locations indicated at "B" and "D", in Figure 4a, which is 25 perpendicular to the scanning surface or scan area 28, then the patterns shown in Figure 4d (a top view of the pattern) and Figure 4e (a side view of the pattern) are obtained. Here, the focal points are indicated at 40, 41 and 42. As shown in Figure 4d, the focal points 40, 41 and 42 are each in an 30 individual plane 40', 41' and 42' which are spaced apart corresponding to the spacing of the fibers in the fiber bundle tip 12. The planes 40', 41' and 42' are perpendicular to the axis 20. In Figures 4b to 4e, arrows 44 indicate the direction of the radial scan.

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For the linearly translated system shown in Figure 1d, there are no "dead spaces" and thus linear translation can produce images suitable images approximately 2 mm by 2 mm in size.

In the exemplary design of the endomicroscopic system, the maximal speed of tissue motion, due to physiological motion, was chosen as 5 mm/s for *in vivo* imaging. A near diffraction-limited focusing lens (i.e. a lens which approximates an ideal lens by providing very small focal points) was chosen as the focusing lens 14. The near diffraction-limited focusing lens was supplied by Melles Griot Inc. In addition, each single mode fiber, from the plurality of single mode fibers 10, had a core diameter of 5 microns (i.e.  $\phi_c \approx 5 \mu\text{m}$ ) and was operated at a wavelength of 0.86  $\mu\text{m}$ . Furthermore, the design incorporates an approximate core index of  $n_c = 1.447$  and a difference in the refractive index between the core and the cladding of  $\Delta n = 0.005$ . Using these values, the NA of the fiber is then given by:

$$NA \approx n_c(2\Delta n)^{1/2} = 0.145 \quad (1)$$

and the acceptance angle,  $\theta_a$ , of the fiber is given by:

$$\theta_a = \sin^{-1}(NA) = 8.32^\circ = 0.145 \text{ rad} \quad (2)$$

The design further incorporates the concept of an ideal lens which is used to focus optical radiation, from the plurality of single mode fibers 10, at a magnification of 1 to 1 and that the far field beam divergence angle is similar to  $\theta_a$ . Then, for light beam radiation with a center wavelength  $\lambda_0$ , the beam diameter at the focal point is given by:

$$\phi_f = 2w_0 = 2 \frac{\lambda_0}{\pi\theta_a} = 3.95 \mu\text{m} \approx \phi_c \quad (3)$$

The spot diameter  $\phi_f$  is approximately equal to the core diameter ( $\phi_c = 5 \mu\text{m}$ )

which results in efficient optical coupling. The depth of focus is  $2 \frac{\pi w_0^2}{\lambda_0} = 27.2$

mm and the beam diameter at the ends of the focal zones for focal points 36, 37 and 38 is given by:

$$\phi_f' = 2\sqrt{2} w_0 = 5.59 \text{ mm} \quad (4)$$

Since the  $\phi_f$  and  $\phi_f'$  parameters are defined in terms of amplitudes, within 40  $\mu\text{m}$  of the focal point in the axial direction, the beam diameter based on

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light intensity (i.e. the square of the light amplitude) may actually be smaller than 5  $\mu\text{m}$ .

The above calculation is based on ideal optics operating on the principle optical axis. Using an off-the-shelf lens system with  $\varnothing = 5 \text{ mm}$ ,  $f = 5 \text{ mm}$ , and a working distance of 8.2 mm, it has been found that the off-axis angle required to cover a 2 by 2 mm image is about 5° using commercial ray-tracing software. At approximately an 80% fill factor of the focusing lens 14, the ray-tracing results show the on-axis RMS focal point to be 5.3  $\mu\text{m}$  in radius, and the 5° off-axis RMS focal point to be 10.3  $\mu\text{m}$  in radius. A custom designed lens system should have better performance.

As illustrated in Figure 1, the working distance of the entire optical system, i.e. the distance from the focusing lens 14 to the focal point of the apparatus is determined by the focal length of the lens system, the diameter of the focusing lens 14 and the gap between the focusing lens 14 and the mirror 16. Using the off-the-shelf lens system discussed above, the working distance is about 2.35 mm. The distance from the center of the image to the rotational axis of the mirror 16 is about 5.47 mm. To obtain a 2 mm scan in the radial direction, the sector scanning angle should be approximately  $\pm 10.4^\circ$ , or about 20° in total, as determined by the geometry of the optical system.

Currently existing *in vivo* OCT systems perform radial scans at 4 to 8 revolutions per second (RPS) to yield a biologically acceptable 4 to 8 frames per second. For the design of the present embodiment, 4.4 RPS is chosen as the rotational speed. The rotational speed depends on the repetition rate of the A-scans and the number of A-scans required to obtain a 5  $\mu\text{m}$  lateral resolution. Therefore, the imaging speed of the apparatus of the present invention is 4.4 frames/s while other imaging speeds may be chosen based on different end-user applications. The imaging time for each individual frame is 12.6 ms, as determined by the rotation speed and the sector scanning angle. Therefore, for a given frame, the system is acquiring signals for 12.6 ms and the time between frames is about 215 ms during which data processing is performed. These parameters are dependent on

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the performance of the optical delay generator (which is described later) that is used in the system.

While the above calculations were made based on a light source operating at a light wavelength of 860 nm and custom made single mode fibers, implementation using a light source operating at other wavelengths, such as 1300 nm, and off-the-shelf fiber may also be possible. Figure 5a shows a beam spot diagram for a 5 channel fiber bundle tip operating at a wavelength of 1300 nm and using off-the-shelf fibers (Corning SMF-28). The fiber bundle tip has a fiber step size of 125  $\mu\text{m}$ . The light beams from these fibers, focused by a lens having a 5 mm diameter and a 4.5 mm focal length, cover a focal zone of approximately 0.65 mm. The resulting lateral imaging resolution is approximately 10  $\mu\text{m}$ . Figure 5b shows a beam spot diagram for a 15 channel fiber bundle tip operating at a wavelength of 890 nm and using custom designed fibers having a core diameter of 5  $\mu\text{m}$  and a cladding diameter of 40  $\mu\text{m}$ . This fiber bundle tip has a fiber step size of 40  $\mu\text{m}$ . The beams spots of only the central 5 channels are shown. The resulting lateral imaging resolution is approximately 5  $\mu\text{m}$  over a focal zone of approximately 0.65 mm.

Figure 5c shows beam spot diameter versus distance along the focal zone for the 5 channel fiber bundle tip of Figure 5a. Figure 5c shows that the beam spot diameter is consistently less than 15  $\mu\text{m}$  over the entire 0.65 mm focal zone. Figure 5d shows beam spot diameter versus distance along the focal zone for the 15 channel fiber bundle tip of Figure 5b. Figure 5d shows that the beam spot diameter is approximately 5  $\mu\text{m}$  over the entire 0.65 mm focal zone.

Referring now to Figure 6, the overall general layout of the basic optical elements of the apparatus of the present invention comprises a plurality of optical sources 50, a plurality of tree couplers 52, a plurality of dB couplers 54, a fiber bundle tip 56, a plurality of detectors 58, a plurality of demodulators 60 and an optical delay generator 64. The plurality of optical sources 50, which may be lasers, are connected to the plurality of tree couplers 52. More than one laser may be needed to ensure that

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adequate optical radiation is provided to each of the fibers (i.e. channels) in the tip 56. Each tree coupler 52 couples a respective optical source 50 to a subset of the plurality of 3 dB couplers 54. The plurality of 3 dB couplers 54 are connected to the fiber bundle tip 56 for onward transmission of approximately half of the light radiation from the plurality of optical sources 50. The fiber bundle tip 56 includes fiber bundle tip 12 and the other optical elements of Figure 1 (i.e. the focusing lens 14 and the mirror 16). The other half of the radiation from the plurality of optical sources 50 is reflected back to detectors 58 which in turn are connected through the demodulators 60 to a computer 62 which functions to process the sampled data to generate the B-scan image 30. The optical delay generator 64 is used by the 3 dB couplers 54 to provide a delayed reflected signal to the detectors 58. The sample being investigated by the tip 56 is indicated at 65.

In the layout shown in Figure 6, 1 dB or 10 dB optical couplers and the like may be used in place of the 3 dB couplers 54. Furthermore, the intensity of the optical radiation transmitted to each of the 3 dB couplers 54, and consequently each fiber, by the tree couplers 52 need not be the same and in fact is chosen depending on whether the 3 dB coupler provides optical radiation to a fiber (i.e. channel) that facilitates a deep or shallow scan into the tissue. High intensity optical radiation is needed to scan deeply into the tissue. Accordingly, tree couplers 52 and 3 dB couplers 54 that feed optical radiation to fibers that scan deeply into the tissue are adapted to provide larger amounts of optical radiation.

Figures 7a and 7b show the optical delay generator 64 in greater detail. The optical delay generator 64, similar to those in existing *in vivo* OCT systems, is used to perform the A-scans using the coherence envelope of each individual fiber. The optical delay generator 64 comprises a grating 66, a lens 67, a scanning mirror 68 and a mirror 70. Rapid depth scanning can be achieved with the optical delay generator 64 by dispersing quasi-monochromatic light from the multiple single mode fibers 10 in the fiber bundle tip 12 onto the diffraction grating 66 and focusing the dispersed light onto the oscillating mirror 69. This has the effect of applying a linear ramp in the frequency or Fourier domain as described by G. J. Tearney,

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B.E. Bouma and J. G. Fujimoto ("High-speed phase and group delay scanning with a grating based phase control line" *Nature Medicine* 4(7), 861-865 (1998)). With recombination of the reflected wavelengths at the diffraction grating 66, a real space-time delay is created. The angle of the scanning mirror 68 is rapidly oscillated through several degrees of rotation creating a rapidly varying time delay in the reference arm which allows for fast, repeated depth scanning of a sample.

The optical radiation 70 from one fiber from the multiple single mode fibers 10 is shown in Figure 7a. The optical radiation 70 is dispersed into spectral components represented by spectral components 71, 72 and 73 by the grating 66. Spectral component 71 represents the lowest wavelength in the optical radiation 70; spectral component 73 represents the highest wavelength in the optical radiation 70; and spectral component 72 represents the center wavelength in the optical radiation 70. These spectral components of the optical radiation 70 are vertically aligned in the optical delay generator 64. In a similar fashion, optical radiation from other fibers from the multiple single mode fibers 10 are dispersed and vertically aligned, with a vertical spacing between the dispersed optical radiation from the different fibers. The offset of the center wavelength of the dispersed optical radiation from the pivot axis of the scanning mirror 68, for a given fiber, is represented by  $x_d$  which facilitates phase modulation of the dispersed optical radiation from each of the multiple single mode fibers 10. Alternatively, if  $x_d$  were zero then a phase modulator would be needed, for each of the single mode fibers 10, to phase modulate the optical radiation from each of the single mode fibers 10. This has the advantage of allowing for a reduction in size of the scanning mirror 68 which in turn allows for a higher frame rate to be used. Furthermore, the phase modulator is electrically controlled which allows for very stable signals are generated

Referring now to Figure 7b, the multiple single mode fibers 10 are aligned in the fiber bundle tip 12, such that dispersed optical radiation from each of the multiple single mode fibers 10 is vertically aligned on the scanning mirror 68 as rows 75, 76, 77 and 78. Alternatively, other ordered arrangements may also be used for the spectral components of the optical

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radiation from each fiber from the multiple single mode fibers 10 such as columns.

As illustrated in Figure 6, a single optical delay generator may be used to introduce delay in multiple fibers. The limiting factor in determining the number of channels that may be coupled to a single optical delay generator is the physical size of the scanning mirror which is in turn limited by the resonance frequency of the optical delay generator. Commercially available resonance optical scanners can operate up to 16 kHz. Accordingly, a size of 4 mm by 5 mm may be used for the scanning mirror 68. Since the fiber bundle array is about 2 mm in size, it is possible to fit the entire array onto one optical delay generator. Therefore, for the embodiment of the present invention, a single optical delay generator is used having an optical scanner operating at  $f_r = 16$  kHz with an optical scan angle  $\alpha$  of  $\pm 2^\circ$ . The embodiment also incorporates a grating pitch of  $p = 3.33 \mu\text{m}$ , a center wavelength of  $\lambda_0 = 0.86 \mu\text{m}$  and a focal length of  $f_i = 21$  mm. Accordingly, the free space group path length difference  $\Delta l_g$  is given by (from Rollins et al. 1998):

$$\Delta l_g = 4\alpha(f_i \frac{\lambda_0}{p} - x_d) = 0.618 \text{ mm} \quad (5)$$

which is also 1.24 mm peak to peak. In equation 5,  $x_d \approx 1$  mm is the displacement between the  $\lambda_0$  spectral line and the pivoting axis on the resonance mirror. The peak A-scan speed is given by:

$$V_{A\max} = 2\pi\Delta l_g f_r = 62.1 \text{ m/s} \quad (6)$$

and the A-scan speed varies according to equation 7.

$$V_A = V_{A\max} \cos(2\pi f_i t) \quad (7)$$

Choosing a source with a coherence length  $l_c$  of 5  $\mu\text{m}$  and a Gaussian emission spectrum, the equivalent emission bandwidth is given by:

$$\Delta\lambda = \beta \frac{\lambda_0^2}{l_c} = 98 \text{ nm} \quad (8)$$

where  $\beta = 0.66$  for a Gaussian envelope.

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The size of the resonant mirror is determined next. For an optical delay generator with a grating having a first order diffraction, the diffraction angle is given by:

$$\theta(\lambda) = \sin^{-1}(\lambda/p) \quad (9)$$

- 5 The spread of the spectrum from  $(\lambda_0 - \Delta\lambda/2)$  to  $(\lambda_0 + \Delta\lambda/2)$  at the Fourier plane of the lens is given by:

$$\Delta x \approx 2f_l[\theta(\lambda_0 + \Delta\lambda/2) - \theta(\lambda_0 - \Delta\lambda/2)] = 1.3 \text{ mm} \quad (10)$$

Since the mirror width is 4 mm, one can fit the spectrum on one side of the resonant mirror with the displacement  $x_d$  having a value of approximately 1 mm. This is illustrated in Figures 7a and 7b. The carrier frequency of an individual channel of the system is given by (Rollins et al. 10 1998):

$$f_c = (4x_d \alpha 2\pi f_l / \lambda_0) \cos(2\pi f_l t) \quad (11)$$

which is 16.3 MHz at the maximum.

- 15 The bandwidth of the interferogram (i.e. the interference fringe pattern) is given by:

$$\Delta f = \frac{\Delta\lambda}{\lambda_0^2} 4\pi \alpha f_l 2(f_l \lambda_0 / p - x_d) \cos(2\pi f_l t) \quad (12)$$

which is 8.4 MHz at the maximum.

Since  $f_c(t) > \Delta f(t)$ , proper demodulation can be performed by conventional rectifying and low-pass filtering, although a sharp frequency cut-off is needed. It is preferable to set up the individual channels of the system such that  $D_A = 40 \mu\text{m}$  (the depth of the A-scan performed by a single channel) coincides with the maximum carrier frequency, so that the variation in carrier frequency over  $D_A$  is minimized. The carrier frequency varies 20 sinusoidally in time given by:

$$\Delta f_c = f_c \{1 - \cos[\sin^{-1}(D_A/\Delta l_p)]\} = 34 \text{ kHz} \quad (13)$$

which is about 0.2% of  $f_c$ .

At other locations, the signal can still be properly demodulated, but the variation in carrier frequency will be larger. The demodulators 60 30 may incorporate an analog high-speed rectifier and a 10-pole low-pass filter to demodulate the signal. Effectively, the signal is frequency down-shifted

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such that the signal is centered at DC and has a bandwidth of  $\Delta f$ . The demodulated envelope signal is then digitized at an appropriate sampling rate. Current existing data acquisition (DAQ) cards operate at 30 MegaSamples per second (MS/s) with an SNR of about 60 dB. Choosing a Gaussian shape for the interferogram spectrum with  $\Delta f = 8.4$  MHz, the 60 dB point is at about 14.5 MHz. Accordingly, the Nyquist rate for digitizing such a signal is approximately 29 MS/s. Therefore, current existing DAQ cards will be able to digitize the envelope signal without aliasing.

Given a sampling rate of 30 MS/s for digitizing the envelope signal at the maximum carrier frequency, the spatial sampling interval in the axial direction is:  $\Delta_{\text{axial}} = V_{A\text{max}}/S = 2.07 \mu\text{m}$ . As shown in Figure 8, a scan path 80 is indicated showing A-scans alternately going up and down through the sample. Sampling points are indicated at 82. The axial spacing of 2.07  $\mu\text{m}$  is indicated at 84. The spatial sampling interval in the lateral direction is determined by the lateral or B-scan velocity and the resonant frequency of the optical scanner in the optical delay generator 64. At the center of the image, where the radial distance  $r$  is 5.47 mm from the rotational axis of the mirror, the radial sampling interval is given by:

$$\Delta_{\text{radial}} = \frac{V_{\text{radial}}}{2f_r} = \frac{2\pi\omega r}{2f_r} = 4.73 \mu\text{m} \quad (14)$$

This interval is indicated at 86 in Figure 8. For the fiber scanning the shallowest depth, the spatial lateral sampling interval is 3.86  $\mu\text{m}$  and for the deepest channel it is 5.59  $\mu\text{m}$ . Therefore, the pixel size at the center of the image is 2.07 by 4.73  $\mu\text{m}$  in the axial and lateral direction respectively. The lateral pixel size varies across the depth of the image from 3.86 to 5.59  $\mu\text{m}$ . By varying the rotational speed of the mirror 16, the lateral sampling interval can be changed, at the expense of frame rate. If a higher resonance frequency optical scanner is used, the sampling interval may also be reduced.

For a pulsed optical source (e.g. a 15 to 20 fs pulsed laser emitting light with a wavelength of 860 nm), the coherence length will be approximately 4.5 to 6  $\mu\text{m}$ . Since the spatial sampling interval in the axial

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direction is about 2  $\mu\text{m}$ , which is smaller than half of the coherence length, the image is reasonably sampled in the axial direction. Using a near diffraction-limited focusing lens as the focusing lens 14, the beam spot size should be about 5  $\mu\text{m}$ . Since the spatial sampling interval in the lateral direction varies from 3.86 to 5.59  $\mu\text{m}$ , the image is slightly under sampled, given that the beam waist size is about 5  $\mu\text{m}$ . However, the spatial sampling interval is not equivalent to the final image resolution, which is also influenced by local contrast and noise levels. Local contrast is the difference in reflectivity between two points in the sample that show up as adjacent pixels in the image. If the two points have similar reflectivity, i.e. low local contrast, it will be difficult to resolve these points.

10 Imaging speed should be fast enough to reduce motion blurring. Given that the target speed (i.e. tissue motion) is typically 5 mm/sec, then within a frame time (an elapsed time of 12.6 ms), the target can move up to 15 63  $\mu\text{m}$  in a particular direction which is much larger than the designed 5  $\mu\text{m}$  resolution. In the present embodiment, the A-scan is performed simultaneously in all channels such that one line of the image is formed within 0.6  $\mu\text{s}$  which is the time required to scan the coherence gate through 20 a 40  $\mu\text{m}$  distance. The time between two consecutive A-scans is about 16  $\mu\text{s}$ , which is determined by the rotational speed of the mirror 16 of the system and the number of A-scans per image. Thus, the resultant image should be crisp since the motion during 16  $\mu\text{s}$  is 0.08  $\mu\text{m}$  which is much less than the resolution. Accordingly, there should be no motion blurring in the image but a motion artifact may still exist. The resultant motion artifact may 25 be a geometric deformation of the features being imaged that may be as large as 63  $\mu\text{m}$  depending on the size of the feature and the target velocity. This motion artifact is due to the effect that the air-tissue interface has on the optical radiation from the plurality of optical sources 50.

As illustrated in Figure 9, the focal point of an individual fiber of 30 the apparatus, inside the tissue being imaged, can vary depending on the distance  $d_b$  of the location of the focal point in the tissue, whether the tissue surface had a refractive index of 1, and the actual refractive index of the

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tissue (which is typically approximately 1.4). Accordingly, the actual focal point is at a distance  $d_f$  below the tissue surface given by:

$$d_f = d_o \frac{\tan \theta_1}{\tan \theta_2} = d_o \frac{\tan \theta_o}{\tan \left[ \sin^{-1} \left( \frac{n_1}{n_2} \cdot \sin \theta_o \right) \right]} \quad (15)$$

where  $\theta_f$  is assumed to be equal to  $\theta_o$ , the acceptance angle of the individual fibers and  $\theta_2$  will be determined by the refractive index  $n_1 = 1$  (i.e. air) outside the tissue and  $n_2 = 1.4$  inside the tissue.

The coherence gate location varies according to:

$$d_c = \frac{n_1}{n_2} d_o \quad (16)$$

Accordingly, due to the fact that optical radiation travels more slowly in a medium with a larger refractive index there is an optical path mismatch between the focal point and the coherence gate of an optical beam which is matched in a medium with  $n_f = 1$  (i.e., with no tissue present). This mismatch is:

$$\Delta d = n_2(d_f - d_c) = \frac{n_2 d_o \tan \theta_o}{\tan \left[ \sin^{-1} \left( \frac{\sin \theta_o}{n_2} \right) \right]} - d_o \quad (17)$$

A tissue refractive index of  $n_2 = 1.4$  yields  $\Delta d = 0.97 d_o$ . This mismatch problem is common for all high-NA OCM systems and many existing high-NA OCM systems use some form of dynamic compensation, i.e., changing the reference path length dynamically to compensate for  $\Delta d$ ; however, such dynamic compensation is difficult with a high imaging speed. Accordingly, one aspect of the embodiment of the present invention is to use 'flexible triggering' of the detected interferogram signal.

As shown above, the free space group path length difference is  $2\Delta l_g = 1.24$  mm peak to peak, which is much larger than the useful A-scan range of only 40  $\mu\text{m}$ . This leaves room for dealing with the mismatch since one then can trigger to obtain the interferogram only when the coherence gate is passing through the focal point.

As shown in Figure 9, the working distance for each fiber channel,  $d_w$ , varies with  $n_2$  which is approximately constant. Therefore, if one knows

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where the tissue surface is,  $d_0$  can be determined and in turn  $\Delta d$  can be determined.

Referring to Figure 10, showing a perspective view of a tissue surface and an arbitrary axial line 90, channel 1, which is designated to scan the surface of the tissue, is the first to pass through the axial line 90, in the scan area 28. The focal points of channels 1 and 2 are indicated at 91 and 92 in a schematic representation 94 of the optical radiation from the multiple single mode fibers 10 (i.e. channels) passing through the axial line 90. The focal point of the last channel, i.e. channel 50 in this example, is indicated at 95 and is designated to scan the deepest layer of the tissue in the image. The overall profile of the representation 94 defines a flexible trigger zone, within which the coherence gate and the focal length can be matched. One of the 50 channels, i.e. channel "v", will experience a large and distinctive specular reflection since the air-tissue interface approximates a mirror and reflects incident light. Underneath the tissue surface, the tissue acts as a turbid media which scatters and absorbs incident optical radiation. Thus, channel "v" will determine  $d_0$  for this particular axial line 90 since all of the channels before channel "v" will return a signal that is at noise level. Accordingly, the "flexible triggering" method comprises comparing the detected reflected optical radiation for adjacent channels to locate the tissue surface by identifying the channel in which there is a large increase in reflectance compared to its 'neighboring' channels. This information is then passed on to each of the subsequent channels and the trigger point for each channel is set accordingly to reduce mismatch between the focal point and the coherence gate.

As an example, if channel "v" is channel 13 then the apparatus is calibrated such that channels 1 to 12 are set to scan free space above the tissue surface, channel 13 to scan the tissue surface, and subsequent channels are set to scan deeper tissue, with no mismatch between the focal point and the coherence gate of the optical beam of each channel. During imaging, a tolerance of  $\Delta d_0 = \pm 0.5$  mm of the location of the tissue surface can be allowed as indicated at 96 in Figure 10. This tolerance is related to

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the A-scan performance and the frequency response of the envelope detector as will now be explained.

Given  $\Delta d_0 = 0.5$  mm, the mismatch that needs to be compensated for is given by:

$$\Delta d' = 0.693 \times 0.5 = 0.347 \text{ mm} \quad (18)$$

This means that instead of triggering the interferogram signal at the maximum carrier frequency, the actual carrier frequency needs to be:

$$f_c' = f_{c\max} \cos(\sin^{-1}(\Delta d'/\Delta d_0)) = 13.5 \text{ MHz} \quad (19)$$

which is about 83% of the maximum carrier frequency with the interferogram signal bandwidth changing accordingly. Although the envelope detector's frequency response can be tuned dynamically, it is simpler and faster for the envelope detector to have a fixed response but it was designed for a 17% tolerance of the cut-off frequencies. In this way, the entire flexible triggering scheme contains only fixed components and all of the compensation is performed electronically to satisfy the high imaging speed requirement.

The optical components shown in Figure 6 can be chosen as follows. Based on Boppart, S.A., Bouma, B.E., Pitris, C., Southern, J.F., Brezinski, M.E., and Fujimoto, J.G. (*In vivo Cellular Optical Coherence Tomography Imaging*, Nature Medicine, Vol. 4 No.7:861-865, July 1998), an SNR of greater than 100 dB can be achieved in a non-endoscopic OCT system using 2 mW of incident power on the tissue to allow for imaging to a depth of approximately 2 to 3 mm. The optical source used was a Kerr-lens mode-locked solid-state Cr<sup>4+</sup>: forsterite laser operating at a 1280 nm center wavelength with a coherence length of 5.1 μm. However, the embodiment of the present invention is not limited to this type or any other particular type of source, such as a broadband superluminescent diode. For instance, another possibility is a white-light emission Cr:LISAF optical source with a bandwidth of approximately 100 nm centered at 860 nm which will provide a coherence length of approximately 4.5 to 6 μm. This diode-pumped, solid-state, mode-locked laser should operate with a pulse-repetition rate of about 100 MHz and an average power of 30 mW when operated at 860 nm.

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The pulse energy variation should be less than 1%. Several (e.g., 2 or 4) of these lasers as indicated at 50 in Figure 6 are needed to provide the total power requirement of the 50 channels. The channels scanning the deeper portion of the tissue will need about approximately 1 to 2 mW of incident power per channel and the channels scanning the shallower portion will need less. The tree couplers 52 can be configured to split the source power to match these requirements. Since the maximum carrier frequency is 16.3 MHz, each interference fringe will contain at least 6 laser pulses. Therefore the fringe pattern should be adequately sampled.

For each channel, a separate photo receiver or detector 58 may be used to detect the interference fringes. The maximum detector bandwidth is 125 MHz, although in the apparatus of the present invention, a detector bandwidth of 30.8 MHz may be sufficient, as determined by the carrier frequency and the bandwidth of the interferogram.

An alternate embodiment of the present invention involves the concept of sharing optical components to reduce device complexity and cost. Referring to Figure 11a, a typical single channel interferometer 150 with balanced detection in which the AC component of the interferogram is separated from the DC component of the interferogram and only the AC component is amplified is shown. The single channel interferometer 150 comprises an IR broadband light source L, a visible wavelength guide light G, a balanced detector BD, a polarization controller PC, a phase modulator MOD and an optical delay generator ODG which are connected through a network of optical fibers and 3 dB couplers 140, 142 and 144. The "X" denotes a dead end in the fiber network. The visible wavelength guide light G may be a green laser which indicates the direction in which the single channel interferometer 150 is pointing (i.e. it indicates what will be imaged). The single channel interferometer 150 is connected to a sample S.

The design of Figure 11a can be extended to construct a two channel interferometer 160 as shown in Figure 11b. The subscripts denote the components that are in the two channels. A component without subscripts indicates that the component is used in both channels. The two

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channel interferometer 160 comprises a laser L', a visible wavelength guide laser G', a 2 to 1 tree coupler TC1, polarization controllers PC<sub>1</sub>, PC<sub>2</sub> and phase modulator φMOD', variable delay elements VD<sub>1</sub> and VD<sub>2</sub>, an optical delay generator ODG', detectors BD<sub>1</sub> and BD<sub>2</sub> and 3 dB couplers 162, 164, 166, 168, 170 and 172. The variable delay elements VD<sub>1</sub> and VD<sub>2</sub> are introduced to adjust the coherence gate positions for each channel. The two channels are coupled to samples S<sub>1</sub> and S<sub>2</sub> which may be two points at different locations in a tissue sample. The light source L' is shared between the two channels in this case, with the optical power in channel 1 being twice that in channel 2. Therefore, channel 1 should be used to scan a deeper region of tissue than channel 2. The 1 to 2 tree coupler TC1 is used so that both channels can share the same reference arm (comprising the phase modulator φMOD' and the optical delay generator ODG'). The ability to share the same reference arm allows one phase modulator to be used to phase modulate the optical radiation from the multiple single mode fibers 10 (i.e. all the channels). Note that the two channels are combined into one fiber by the tree coupler TC1 and then fed to the same phase modulator φMOD'. Accordingly, cost and complexity of the two channel interferometer 160 is reduced.

Based on Figure 11b, it is conceivable that a general optical network can be used to construct an N channel OCT system such as optical network 180 shown in Figure 11c. The optical network 180 comprises an optical network for an n<sup>th</sup> channel 182 and a reference arm 184 that is shared by all n channels. The optical network for the n<sup>th</sup> channel 182 comprises a detector BD<sub>n</sub>, 3 dB couplers 194, 196 and 198 and a sample arm comprising a polarization controller PC<sub>n</sub> and a variable delay element VD<sub>n</sub> connected to a sample S<sub>n</sub>. The optical network for the n<sup>th</sup> channel 182 receives optical source radiation 186 from the n-1<sup>th</sup> channel and transmits optical source radiation 188 to the n+1<sup>th</sup> channel via 3 dB coupler 194. The optical network for the n<sup>th</sup> channel 182 receives guide light power 190 from the n-1<sup>th</sup> channel and sends guide light power 192 to the n+1<sup>th</sup> channel via 3 dB coupler 196. In this embodiment, a light source (not shown) may be

shared between each of the N channels with a power distribution that follows a geometric series or another suitable power partition scheme. The reference arm 184, comprising an N to 1 tree coupler TC<sub>n</sub>, a phase modulator "MOD" and an optical delay generator "ODG", is shared between 5 each of the N channels.

Each of the schematics shown in Figures 11a, 11b and 11c, suffer from the fact that a portion of the optical radiation of the interference pattern, from the interference between the reflected optical radiation from 10 the sample and reference arms, which is sent from the 3 dB coupler connected to the detector is lost. In this case 50% of the optical radiation of 15 the interference pattern is lost since a 3 dB coupler is used. For instance in Figure 11a, only 50% of the optical radiation of the interference pattern is sent from 3 dB couplers 140 and 142 to the detector BD. This makes it more difficult to detect the interference pattern especially for interference patterns with low intensities. To address this, a non-reciprocal optical device, such as an optical circulator may be used to send, to a detector, the portion of the optical radiation that would have been lost if only a 3 dB coupler were used.

Referring to Figures 12a, 12b and 12c, alternate embodiments of 20 a single channel OCT device 200, a two channel OCT device 210 and an optical network for an N channel OCT device 220 are shown comprising optical circulators. In Figures 12a, 12b and 12c, the optical circulators C, C<sub>1</sub>, C<sub>2</sub> and C<sub>n</sub> are used to salvage and direct the optical radiation of the interference pattern to the detectors BD, BD<sub>1</sub>, BD<sub>2</sub> and BD<sub>n</sub> respectively to 25 provide a larger intensity interference signal for detection. The rest of the components in these embodiments are similar to those in the of the single channel OCT device 150, the two channel OCT device 160 and the optical network for the N channel OCT device 180 shown in Figures 11a to 11c. The concept of using optical circulators to salvage optical radiation and 30 provide the salvaged optical radiation to a detector may also be applied to the apparatus of Figure 6 in which optical circulators could be placed between the 3 dB couplers and the detectors.

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The schematic shown in Figure 11c and 12c leads to an elegant design, however, parallel interferometers that share components (i.e. a phase modulator) may produce prohibitive amounts of channel cross talk which may consequently lead to image degradation. However, with fiber length mismatching between channels, cross talk may be effectively handled. Electronic cross-talk can be handled using standard shielding and grounding techniques. The following describes the optical cross-talk.

Referring now to Figure 13a, a two channel OCT system 230 was assembled to investigate channel cross talk. The two channel OCT system 230 comprises a laser  $L_E$ , detectors  $D_1$  and  $D_2$ , beam splitters  $BS_1$  and  $BS_2$ , a 1 to 2 tree coupler  $TC_E$ , a phase modulator  $PM_E$ , an optical delay generator  $ODG_E$ , beam collimators  $BC_1$  and  $BC_2$  and two mirrors  $S_{1E}$  and  $S_{2E}$  which simulate samples. In the two channel OCT system 230, the desired imaging signals come from the channel 1 and channel 2 optical paths. The desired imaging signal for channel 1 occurs when light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_1 \rightarrow D_1 \quad (20)$$

interferes coherently with light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (21)$$

and is detected by the detector  $D_1$ . The desired imaging signal for channel 2 occurs when light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow S_2 \rightarrow BS_2 \rightarrow D_2 \quad (22)$$

interferes coherently with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow BS_2 \rightarrow D_2 \quad (23)$$

and is detected by the detector  $D_2$ . Furthermore, OCT imaging in the two channels occurs only when the optical distance  $BS_1 \rightarrow S_1$  is equal to the optical distance  $BS_1 \rightarrow ODG_E$  and when the optical distance  $BS_2 \rightarrow S_2$  is equal to the optical distance  $BS_2 \rightarrow ODG_E$ . Otherwise, image degradation could occur from constructive interference of light reflected from two (or more) different paths that are not the desired imaging paths stated above.

Based on the optical network shown in Figure 13a, there may be two major classes of potential cross talk. The primary source of cross talk may be coherent light that is reflected (from a mirror or the sample) from

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one channel's beam splitter into the other channel's beam splitter and detector. Such cross talk would have intensities equal to the imaging signal intensities and could potentially cause significant image degradation. Reflection from one channel to the other could occur at the optical delay generator  $ODG_E$  or at the samples  $S_1$  or  $S_2$ . Therefore, light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_1 \rightarrow D_1 \quad (20)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (24)$$

Alternatively, light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow S_2 \rightarrow BS_2 \rightarrow D_2 \quad (22)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow ODG_E \rightarrow BS_2 \rightarrow D_2 \quad (25)$$

Sample arms 1 and 2 would not normally be separated as they are in Figure 13a because the sample arms would be aimed at different points (i.e. different depths) on a tissue sample. When the samples are not separate, reflection could occur from channel 1 into channel 2 and vice-versa. In such a case, light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow S_2 \rightarrow BS_1 \rightarrow D_1 \quad (26)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (21)$$

Alternatively, light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_2 \rightarrow D_2 \quad (27)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow BS_2 \rightarrow D_2 \quad (23)$$

It should be recalled that reflection may also occur at undesirable locations such as beam splitters and connector insertion points. Conceivably, such reflections may contribute to image noise if the light from these pathways produced interference fringes having a significant intensity. However, this kind of noise may be secondary to the channel cross talk previously described because of its lower intensity.

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Analysis of the system revealed that the worst-case scenario for interference of such back-reflections involves one reflection from a connector. For example, light from the following optical path:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_1 \rightarrow D_1 \quad (20)$$

5 may interfere with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow PM_E \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (28)$$

There are four possible outcomes for the interference of light from any two pathways and the outcome depends on path length difference. Firstly, if the path lengths are identical, then the intensity of the interference fringes at the detector will be greater than the true signal intensity based solely on the sample reflectivity. This sort of image noise would not be detectable as noise and would alter the measured sample intensity throughout the image. Fortunately, the probability of the path lengths matching exactly is remote. A second possibility is that the path lengths could match to within the coherence length of the light source. This situation would result in an increase in the width of the interference fringe envelope and consequently degradation in axial resolution. This situation is unlikely, but it may be detected by measuring the full-width-half-maximum of the mirror surface depth profile. A third possibility involves the path lengths differing by a distance greater than the coherence length of the source  $L_E$  and less than the scanning depth of the optical delay generator  $ODG_E$ . This situation may manifest as two separate coherence envelopes within one depth sweep by the optical delay generator  $ODG_E$ . The final and most likely possibility is that the path lengths differ by more than the scanning depth of the optical delay generator  $ODG_E$  and no noise or extraneous interference fringes will be detected by the system.

The primary type of channel cross talk should be unlikely because of fiber optic manufacturing. Optical path lengths  $BS_1 \rightarrow ODG_E$  and  $BS_2 \rightarrow ODG_E$  are essentially predetermined by the lengths of the fiber pigtailed coming from beam splitters  $BS_1$  and  $BS_2$ . Optical path lengths  $BS_1 \rightarrow S_1$  and  $BS_2 \rightarrow S_2$  are deliberately matched to the predetermined corresponding reference arm lengths. Typically manufactured fiber lengths differed by several tens of millimeters which is at least one order of magnitude greater

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than the scanning depth of the optical delay generator  $ODG_E$ . Therefore, this type of cross talk should not be a problem in a dual channel system.

In the case of insertion point reflections, if the optical distance  $PM_E \rightarrow ODG_E$  matched the path length difference between optical paths 5  $BS_1 \rightarrow S_1$  and  $BS_2 \rightarrow ODG_E$ , then interference fringes and image degradation may occur. Again, this sort of secondary noise should be unlikely because the fiber lengths are about 300 mm while the optical delay generator  $ODG_E$  scans through only a couple of millimeters. Furthermore, the intensity of such interference fringes would be lost in the system noise. 10 Secondly, the equipment used has a maximum 0.6 dB insertion loss (in other words a maximum of reflection of 0.6 dB) and therefore such a signal is below the detection limits used in the setup of Figure 13a.

To demonstrate that two channels can use the same fiber and optical components, the OCT system 230 was evaluated. The sample arm mirrors  $S_1$  and  $S_2$  were placed such that the sample arm optical path length 15 and the optical delay generator  $ODG_E$  reference arm optical path length matched for each channel and a set of interference fringes were seen at each of the detectors  $D_1$  and  $D_2$ . The sample arms for samples  $S_1$  and  $S_2$  were kept separate for alignment purposes and to eliminate the possibility 20 of light from channel 1 reflecting into the fiber containing channel 2 and vice-versa. Although an optical delay generator could be used to produce both phase modulation and group delay (Tearney et al. 1997), with the setup shown in Figure 13a, the optical delay generator  $ODG_E$  was used for group delay (i.e. depth scanning) while the phase modulator  $PM_E$  in the 25 reference arm was used to produce phase delay.

In the experimental setup of Figure 12a, the light source  $L_E$  comprised a 1310 nm, 9 mW light source (model BBS1310) made by AFC Technologies Inc. The central wavelength of the light source  $L_E$  was 1310 nm with a measured spectral spread of  $\pm 40$  nm. The measured coherence 30 length of the light source  $L_E$  was 10  $\mu$ m. The detectors  $D_1$  and  $D_2$  were 155 Mbps Perkin Elmer InGaAs photodiode receivers with a detection band centered at 1310 nm having a bandwidth greater than or equal to 100 nm.

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The phase modulator **PME** was a JDS Uniphase 43 MHz phase modulator. The beam splitters **BS<sub>1</sub>** and **BS<sub>2</sub>** were made by MetroTek. OZ Optics manufactured the beam collimators **BC<sub>1</sub>** and **BC<sub>2</sub>**. Alternate suitable components may be used from these or other suppliers.

5       The optical delay generator **ODGE** dispersed the collimated light using a 150 line/mm diffraction grating blazed for 1310 nm which was made by CVI Spectral Products. A Melles Griot glass doublet lens with a 30 mm diameter and 100 mm focal length was used to focus light onto the oscillating mirror. EOPC (Electro-Optical Products Corporation) 10 manufactured the resonant scanner that operated at 8 kHz and scanned through a  $\pm 1^\circ$  mechanical or a  $\pm 2^\circ$  optical angle. This angular setting corresponded to a depth scan of about 1 mm in the sample arms for the samples **S<sub>1</sub>** and **S<sub>2</sub>**. Scanning depth is an important consideration in terms of mismatching the optical lengths of the two channels. For instance, if the 15 optical path lengths differ by more than 1 mm then cross talk between the two channels should be minimal and proper shielding and grounding techniques should address electronic cross-talk as well.

Figures 13b and 13c show results from experiments conducted 20 on the setup shown in Figure 13a. Figure 13b shows the oscilloscope trace from the detectors **D<sub>1</sub>** and **D<sub>2</sub>** in channel 1 and channel 2. Figure 13b shows that the interference fringes occur at different points in the cycle of the 25 optical delay generator **ODGE** which reflects the slightly different positioning of the two channels within the cycle of the optical delay generator **ODGE**, i.e. the sample arm mirrors **S<sub>1</sub>** and **S<sub>2</sub>** were deliberately offset by a small amount to simulate imaging at different depths. Figure 13b shows that there 30 is a strong imaging signal in each of the channels and no evidence of any cross talk. The arrows **232** and **234** indicate reflection from two different sample points which could correspond to two different points in a tissue sample. Furthermore, the full-width-half-maximum of the envelope of each detected pulse corresponded to the coherence length of the light source **L<sub>E</sub>** which indicates that the light signal in each channel originated from the light source **L<sub>E</sub>**. Figure 13b shows the experimental results when one of the

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sample points was moved relative to the other sample point. In this case, cross-talk was also not observed.

In another embodiment of the invention, the fiber optic network, previously disclosed herein, is incorporated into an endoscope so that the multi-channel OCT methodology may be used clinically. Due to the size of the fiber bundle tip 12 of the apparatus, the fiber bundle tip 12 will not fit into the working channel of a conventional diagnostic endoscope (although it may be incorporated into the larger-diameter therapeutic endoscopes). Therefore, an alternate design approach was taken. Instead of designing the fiber bundle tip 12 to accommodate the working channel of a conventional diagnostic endoscope, all of the functionality of a conventional diagnostic endoscope was designed around the fiber bundle tip 12. As shown in Figure 14, one embodiment of a GI endoscope 300 (corresponding to the tip 56 of Figure 6) incorporating the endomicroscope of the present invention is approximately 11 mm in diameter. This is slightly larger than the conventional diagnostic endoscope which is 8 - 9 mm in diameter. The GI endoscope 300 has the endomicroscopy capability disclosed above in addition to conventional forward-viewing white light imaging. Therefore, a user of the GI endoscope 300 should be able to obtain a 2 by 2 mm cross-sectional image as illustrated in Figure 16.

The GI endoscope 300 includes a 2.7 mm diameter suction/biopsy channel 302. The end of the suction/biopsy channel 302 is bent so as to present an opening 304 directed towards the tissue area of interest 306. The axis of the suction/biopsy channel 302 may be on the order of 6.7 mm from the center of the tissue area of interest 306. Two channels 308 and 310 are provided for white light illumination and a channel 312 is provided for white light endoscope forward viewing. Each of the channels 308, 310 and 312 may have a diameter of 2.7 mm. A small channel 314 is also provided for an air or water nozzle.

In accordance with the present invention, a side-viewing Endoscopic Coherent Optical Microscope (ECOM) 316 is provided in the GI endoscope 300. The side-viewing ECOM 316 includes a drive mechanism 318 for rotating the mirror 16 (not shown in Figures 14 and 15). As

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mentioned previously, radial, translational or helical scanning may be employed. Furthermore, as previously mentioned, a MEMS drive mechanism may be used instead of a mechanical drive mechanism. The side-viewing ECOM 316 is configured to scan through the tissue area of interest 306 having the depth set by the boundaries 320 and the angular extent set by the boundaries 322. Additionally an optical window 324 may be provided for the side-viewing ECOM 316 (see Figure 14).

The forward-viewing white light channel 312 is updated at a rate of 30 frames/sec. The cross-sectional images obtained by the side-viewing ECOM 316 are updated at 4.4 frames/sec. All imaging channels are displayed simultaneously. The images that may be generated by the GI endoscope 300 are illustrated in Figures 16 and 17. Figure 16 shows a simulated image of a human colon epithelium incorporating the expected spatial resolution which may achievable with the side-viewing ECOM 316. Figures 17a and 17b are a comparison of microscopy imaging versus *in vivo* OCT imaging. Figure 17a has two panels which each show a microscopy image of sweat ducts in the human skin. Figure 17b has three panels which each show an *in vivo* OCT image of sweat ducts in the human skin. The *in vivo* OCT images were generated with a light source operating at a wavelength of 1300 nm.

Typical maneuvers or use of the GI endoscope 300 by an endoscopist will incorporate the following steps:

- a) Following the steps of a general endoscopy procedure, the GI endoscope 300 is inserted under the guidance of the conventional forward-viewing white light channel 312. This maneuver should be no different from that of currently available GI endoscopes.
- b) When the endoscopist needs to make microscopic examinations, he/she first pushes the GI endoscope 300 into contact with the wall of the lumen as shown in Figure 13. The optics are designed such that when the GI endoscope 300 is in contact with the tissue, the correct working distance of the entire optical system is obtained. Although the GI endoscope 300 is in contact with the

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wall, the part of the tissue under microscopic examination is not, as illustrated in Figure 15. Therefore, the surface features of the tissue are not distorted by contact pressure. However, this does not imply that the GI endoscope 300 can only be operated in a contact mode. In fact, the GI endoscope 300 may be operated in a non-contact mode, as long as images are formed, which is dictated by whether the previously described dynamic triggering algorithm has found an air-tissue interface. If the air-tissue interface lies within the working distance of the system then the interface should be specific and easily detected since the interface produces clear peaks in the detected light pattern as previously described in the 'flexible triggering' method.

5  
10  
15  
c) If the endoscopist needs to examine a region adjacent to the area imaged in step (b), then the endoscopist can torque the GI endoscope 300 and rotate the field of view to a new location.

The best techniques currently in use for visualization of the 20 gastrointestinal (GI) tract include endoscopic ultrasonography (EUS) and magnification endoscopy (ME). The resolution of high-frequency EUS, approximately 70 to 100 mm, is insufficient for the identification of many conditions that perturb tissue microstructure, most notably subtle pathologic changes arising within the superficial layers of the GI tract (mucosa and submucosa). ME, with a magnification of up to 170X, provides excellent 25 images of fine superficial mucosal patterns but subsurface structures and lesion staging cannot be determined. Accordingly, tissue biopsy and histology currently remain the standard of care for detecting microscopic diseases involving the GI tract.

The side-viewing ECOM 318 disclosed herein may achieve real-time, 2 mm deep cross-sectional images of the GI wall at a resolution of 5  $\mu\text{m}$  in both axial and transverse (lateral) dimensions. For reference, 30 gastrointestinal epithelial cells average 7 to 10  $\mu\text{m}$  in size which increases further as dysplastic or neoplastic transformation ensues. In the GI tract, a depth of view at 2 mm is nevertheless sufficient to detect mucosally-based

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diseases as well as any neoplastic invasion into the underlying submucosa, which is of important for prognostic and therapeutic purposes. The image resolution of the side-viewing ECOM 316 may correspond to observing an *unstained histology slide under a 100X (total magnification) microscope.* 5 Accordingly, many important entities such as dysplasia (cellular neoplastic alterations) or neoplastic violation of structures such as the lamina propria or muscularis mucosae may be discernible with the side-viewing ECOM 316.

The present invention may allow for *in-situ* diagnosis of diverse 10 microscopic mucosal pathologies and lesion staging. In essence, this "optical biopsy" technique may replace, or at the very least, guide the standard biopsy and histology method. This may translate into reducing unnecessary biopsy samples and tissue processing, decreasing patient risk and increasing sampling rate and diagnostic yield thus providing immediate 15 diagnostic feedback both to the physician and the patient and targeting biopsies (which in itself may become a therapeutic maneuver in some cases). Pre-neoplastic GI conditions such as Barrett's esophagus, chronic ulcerative colitis, early flat adenomas, or foci of aberrant colonic crypts, to name a few, may be applicable to the side-viewing ECOM 316. Currently, 20 detection and surveillance of neoplastic progression within these conditions are suboptimal due to their microscopic nature.

Secondly, the side-viewing ECOM 316 may serve as a functional 25 imaging system permitting monitoring of neoplastic and non-neoplastic tissue alterations over time. For instance, the recovery of the structure of small intestinal villi and reduction in inflammatory cells may be monitored by the side-viewing ECOM 316 in diverse malabsorptive disorders of the gut such as gluten-sensitive enteropathy, tropical sprue and intestinal infestation. The natural history of many mucosal diseases at the microscopic level may also be assessed in a minimally invasive manner. 30 The ability to monitor structural cellular changes that are occurring *in vivo* with time may provide important physiologic information on cellular function and insight into cellular pathologic transformation.

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Thirdly, the side-viewing ECOM 316 may be used in the monitoring of tissue post therapy. *In vivo* microscopic evaluation of surgical resection margins or treatment margins during post-therapeutic surveillance of cancer resection or assessment of the adequacy of photodynamic therapy of mucosal preneoplastic conditions are only some examples.

Applications in other medical specialties may also be possible. It should be understood by those skilled in this art that the multichannel OCT apparatus disclosed herein may have application in a large number of medical specialties such as dermatology, hematology, oncology (medical and radiation), ophthalmology, urology, surgery, respirology and gastroenterology.

The multichannel OCT system disclosed herein may be altered to further improve system performance. For instance a modification that may be made would be to employ coded transmission for the optical radiation which is radiated from the optical sources. This technique may increase the image resolution by increasing the SNR of the optical radiation of the interference pattern obtained in channels which suffer from poor SNR.

It should be understood that various modifications can be made to the preferred embodiments described and illustrated herein, without departing from the present invention, the scope of which is defined in the appended claims. For instance, in each of the schematics, herein disclosed, other optical couplers may also be used in place of the 3 dB couplers.

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**CLAIMS:**

1. An apparatus for optical examination of a sample, the apparatus comprising:
  - 5 an optical source means for providing a plurality of separate optical radiation sources;
  - a first optical path extending from the source means;
  - a focusing means in the first optical path for focusing optical

10 radiation from the optical radiation sources into a plurality of respective focal points located on a surface within the first optical path to provide substantially continuous coverage of a selected portion of the first optical path, whereby, in use, a sample can be located at least partially within said selected portion, thereby permitting simultaneous scanning of a plurality of points within the sample.

15

- 2. An apparatus as claimed in claim 1, wherein the optical source means comprises a primary optical source and optical coupling means connecting the primary optical source to the optical radiation sources and comprising a plurality of optical fibers.

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- 3. An apparatus as claimed in claim 2, wherein the plurality of optical fibers terminate in a fiber bundle tip, wherein ends of the optical fibers in the fiber bundle tip are stepped relative to one another along the first optical path and wherein optical radiation from each optical fiber is focused to a different focal point.

25

- 4. An apparatus as claimed in claim 1, 2 or 3, which includes a rotatable mirror in the first optical path, for deflecting radiation from the optical radiation sources to permit rotational movement of the surface.

30

- 5. An apparatus as claimed in claim 1, 2 or 3, which includes a mirror in the first optical path and wherein the optical source means, the

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focusing means and the mirror, in combination, may be linearly translated to permit linear movement of the surface.

6. An apparatus as claimed in claim 1, 2 or 3, which includes a  
5 rotatable mirror in the first optical path and wherein the optical source  
means, the focusing means and the rotatable mirror, in combination, may be  
linearly translated to permit helical movement of the surface.

7. An apparatus as claimed in claim 4, 5 or 6, wherein the surface is  
10 a complex surface.

8. An apparatus as claimed in claims 4, 5 or 6, wherein the mirror is  
a surface of a prism.

15 9. An apparatus as claimed in claims 4 or 6, including a  
micromachined electro-mechanical system coupled to the mirror for rotating  
the mirror.

10. An apparatus as claimed in claim 5 or 6, including a  
20 micromachined electro-mechanical system for linearly translating the optical  
source means, the focusing means and the mirror.

11. An apparatus as claimed in claim 2, 3 or 4, which further includes  
25 a plurality of optical couplers between the primary optical source and the  
optical fibers, an optical delay generator coupled to the optical couplers and  
detector means coupled to the optical couplers, wherein the optical couplers  
transmit a portion of the radiation from the primary optical source along the  
first optical path and a portion of the radiation from the primary optical  
30 source to the optical delay generator, the optical delay generator providing a  
second optical path, wherein an interference effect occurs between  
radiation returned along the first and second optical paths to the optical  
couplers and the optical couplers transmit the radiation returned along the  
first and second optical paths to the detector means.

12. An apparatus as claimed in claim 11, which includes a plurality of primary optical sources and a plurality of tree couplers, each tree coupler being associated with one primary optical source and coupling said one primary optical source to at least one of the optical couplers.

13. An apparatus as claimed in claim 12, which includes a plurality of optical circulators, placed between the optical couplers and the detectors for providing salvaged optical radiation to the detectors.

10 14. An apparatus as claimed in claim 11, wherein a plurality of optical fibers couple the optical couplers to the optical delay generator, the optical delay generator having a grating and a scanning mirror, the scanning mirror having an axis, wherein the grating separates optical radiation from each  
15 optical fiber into spectral components linearly oriented on the scanning mirror, wherein the midpoint of said spectral components is offset from the axis of the scanning mirror by a distance  $x_d$  to phase modulate said spectral components.

20 15. An apparatus as claimed in claim 11, which includes a first plurality of optical fibers for coupling each optical coupler to a phase modulator and a second plurality of optical fibers for coupling each phase modulator to the optical delay generator, the optical delay generator having a grating and a scanning mirror, the scanning mirror having an axis, wherein  
25 for each optical fiber, the phase modulator phase modulates the optical radiation and said grating separates said phase modulated optical radiation into spectral components which are linearly oriented on said scanning mirror, the midpoint of said spectral components being centered on the axis of said scanning mirror and wherein the spectral components from each  
30 optical fiber is spaced apart from the spectral components of the optical radiation from the other optical fibers.

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16. An apparatus as claimed in claim 11, which includes a plurality of optical fibers coupling each optical coupler to a tree coupler for combining optical radiation from each of the optical fibers into a first optical fiber, said first optical fiber connected to a phase modulator for phase modulating said combined optical radiation and including a second optical fiber for coupling said phase modulator and said optical delay generator.

17. An apparatus as claimed in claims 4, 5 or 6, wherein the apparatus is configured as an endoscope for internal examination of a body, wherein the first optical path, the focusing means and the mirror are provided in the endoscope, and wherein the endoscope includes at least one of: at least one channel for white light illumination; a channel for white light endoscope forward viewing; a channel for one of an air nozzle and a water nozzle; and a suction/biopsy channel.

18. An apparatus as claimed in claim 17, wherein the endoscope is adapted to perform radial, translational or helical scanning.

19. An apparatus as claimed in claim 18, wherein the endoscope further includes a micromachined electro-mechanical system as a drive mechanism.

20. An N channel apparatus for optical examination of a sample, wherein the N channel apparatus comprises a plurality of optical networks and a reference arm, each optical network providing one channel for the N channel apparatus and sharing the reference arm.

21. An N channel apparatus as claimed in claim 20, wherein the optical network comprises a defector, an optical coupling means and a sample arm, wherein the optical coupling means is configured to receive optical radiation from a previous optical network and to transmit optical radiation to a next optical network.

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22. An N channel apparatus as claimed in claim 21, wherein the sample arm comprises a polarization control means, a variable delay element and a sample.
- 5 23. An N channel apparatus as claimed in claim 20, wherein the reference arm comprises a tree coupling means, a phase modulating means and an optical delay means.
- 10 24. A two channel apparatus, for optical examination of a sample, said two channel apparatus comprising two optical networks as claimed in claim 20, 21, 22, 23, an optical source and a visible light source for guiding the orientation of the two channel apparatus.
- 15 25. A method for optical examination of a sample, the method comprising:
- (a) providing radiation from a plurality of separate optical radiation sources, along a first optical path;
- (b) providing focusing means in the first optical path;
- (c) focusing the optical radiation from the optical sources into
- 20 a plurality of respective focal points along a surface within the first optical path to provide substantially continuous coverage of a selected portion of the first optical path; and
- (d) providing a sample located at least partially within the first optical path; and,
- 25 (e) simultaneously scanning a plurality of points within the sample.
26. A method as claimed in claim 25, which includes providing radiation from a primary optical source and transmitting the radiation along a plurality of optical fibers to a plurality of separate optical radiation sources.
- 30 27. A method as claimed in claim 26, which includes terminating the plurality of optical fibers in a fiber bundle tip, providing the ends of the

optical fibers in the fiber bundle tip in a common plane and stepping the ends of the optical fibers relative to one another, along the first optical path, and focusing radiation from the optical fibers through a common lens.

- 5      28.     A method as claimed in claim 27, which includes:  
         (a) providing a rotatable mirror in the first optical path;  
         (b) deflecting the first optical path;  
         (c) causing the plurality of focal points to be located on a surface;  
         (d) performing an axial scan;  
10     (e) rotating the mirror to move the surface; and,  
         (f) repeating step (d) at least two times and performing step (e)  
between each repetition.
- 15     29.     A method as claimed in claim 27, which includes:  
         (a) providing a mirror in the first optical path;  
         (b) deflecting the first optical path;  
         (c) causing the plurality of focal points to be located on a surface;  
         (d) performing an axial scan;  
         (e) linearly translating, in combination, the focusing means, the  
20     plurality of optical radiation sources and the mirror to move the surface; and,  
         (f) repeating step (d) at least two times and performing step (e)  
between each repetition.
- 25     30.     A method as claimed in claim 27, which includes:  
         (a) providing a mirror in the first optical path;  
         (b) deflecting the first optical path;  
         (c) causing the plurality of focal points to be located on a surface;  
         (d) performing an axial scan;  
         (e) simultaneously rotating the mirror and linearly translating, in  
30     combination, the focusing means, the plurality of optical radiation sources  
and the mirror to move the surface; and,  
         (f) repeating step (d) at least two times and performing step (e)  
between each repetition.

31. A method as claimed in claims 28, 29 or 30, which includes providing a surface of a prism as the mirror.
- 5 32. A method as claimed in claims 28, 29 or 30, which includes supplying radiation from the primary optical source through a plurality of couplers to the optical fibers, providing an optical delay generator connected to the optical couplers and providing a second optical path, permitting radiation to be transmitted back along the first and second optical paths to the couplers, for forming interference, and transmitting radiation received from the first and second optical paths at the optical couplers to detection means for detection of the interference pattern.
- 10 33. A method as claimed in claim 32, which includes providing a plurality of primary optical sources and, for each primary optical source, a respective tree coupler, and coupling each primary optical source through said respective tree coupler to each of the optical couplers.
- 15 34. A method as claimed in claim 32, which includes providing optical circulator means between the optical couplers and the detection means for providing salvaged optical radiation to the detection means.
- 20 35. A method as claimed in claim 33, which includes providing the apparatus as an endoscope adapted for examining an internal cavity of the body, including at least one of: at least one channel for white light illumination, a white light endoscope forward viewing channel, a suction/biopsy channel and a channel for one of an air nozzle and a water nozzle.
- 25 30 36. A method as claimed in claims 30, 31 or 32, wherein there is a change in refractive index between a medium containing the optical radiation sources and the sample and for each focal point, a distance mismatch due to the change in refractive index between the coherence gate

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of each optical radiation source and the focal point in the sample due is obtained according to the steps of:

5 (a) scanning optical radiation from the plurality of optical radiation sources in said first optical path such that the focal points of the optical radiation sources are aligned along a path extending from the medium containing the optical radiation sources into the sample;

(b) detecting the reflected optical radiation for each focal point; and,

10 (c) locating the focal point for which there is a large change in reflected optical radiation compared to neighboring focal points, whereby, the focal point located in step (c) indicates the location of the interface between the sample and the medium containing the optical radiation sources.

15 37. A method as claimed in claim 36, wherein the method further comprises repeating steps (a) to (c) for each axial scan to obtain proper spatial resolution for the selected scan zone.

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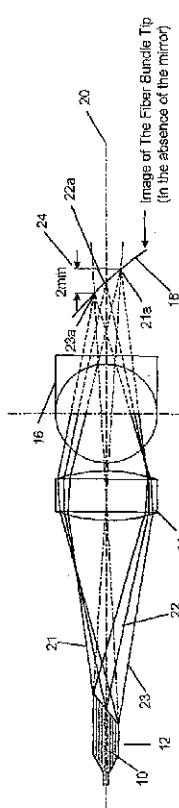


Figure 1a

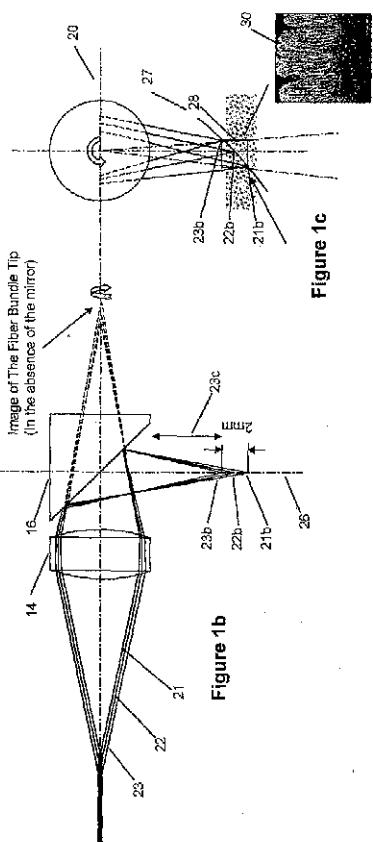
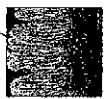


Figure 1b

Figure 1c



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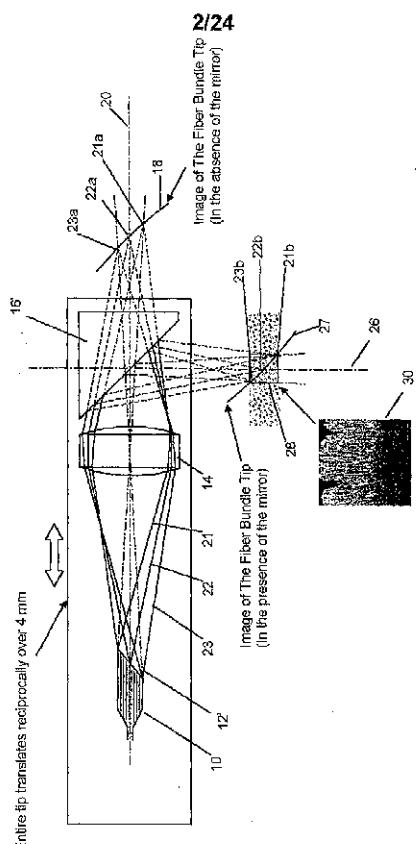


Figure 1d

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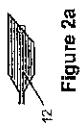


Figure 2a

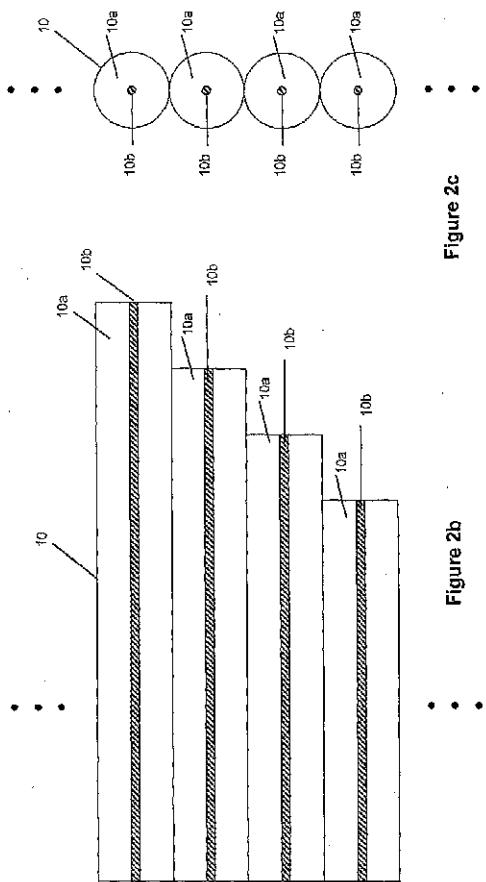


Figure 2b



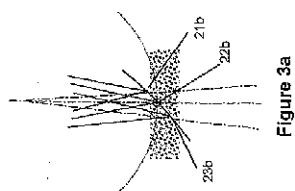
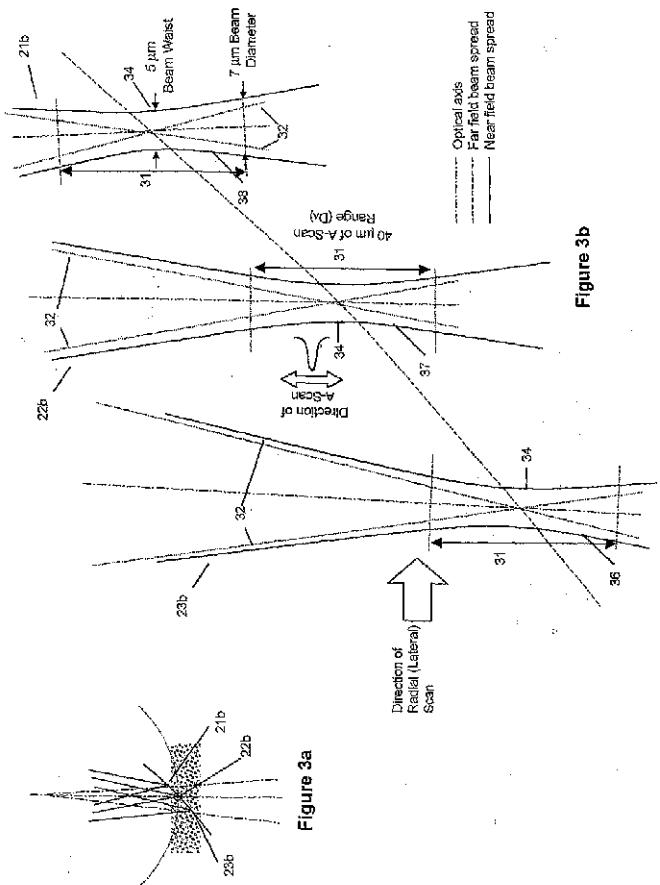
Figure 2c

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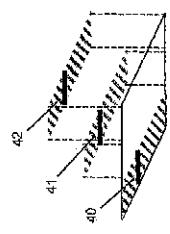


Figure 4f

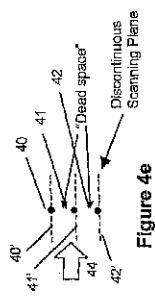


Figure 4e

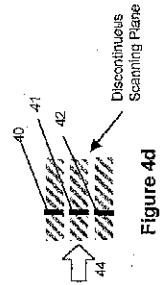


Figure 4d

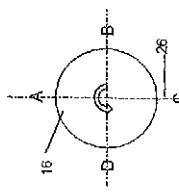


Figure 4a

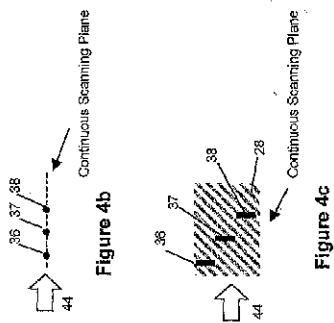


Figure 4b

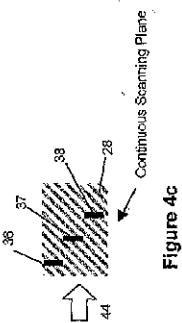


Figure 4c

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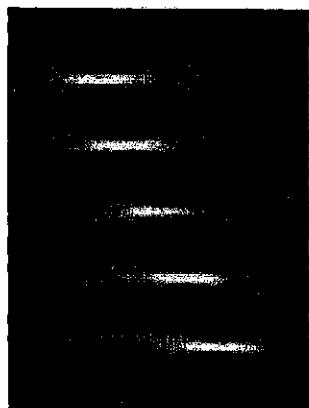


Figure 5b

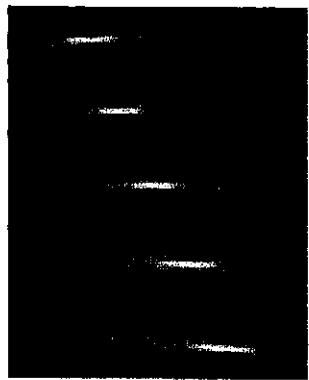


Figure 5a

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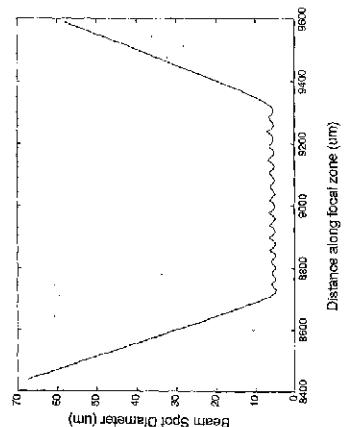


Figure 5d

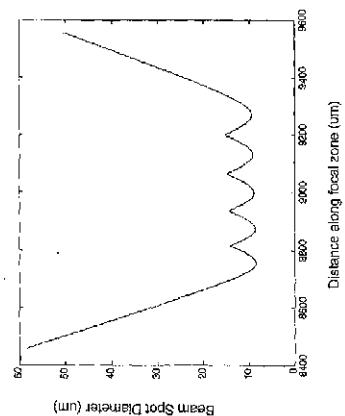


Figure 5c

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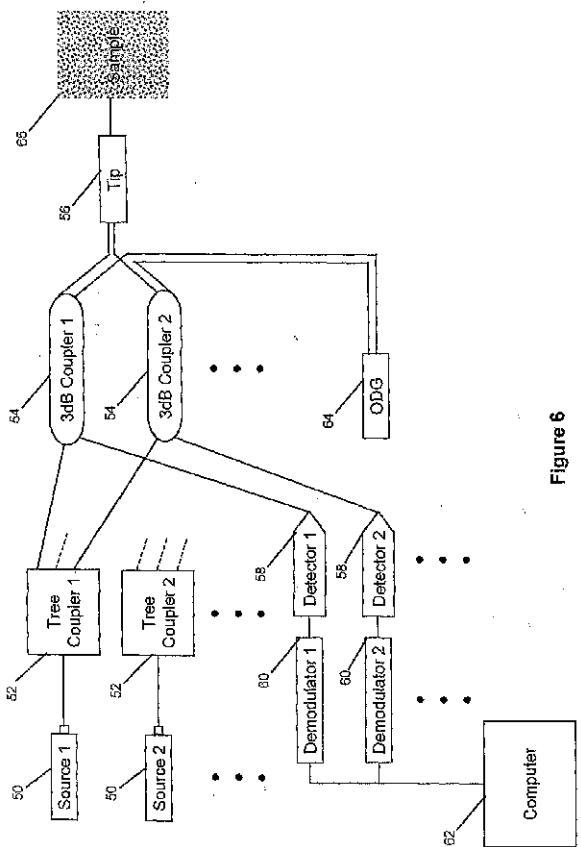


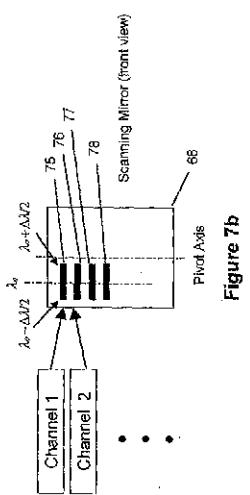
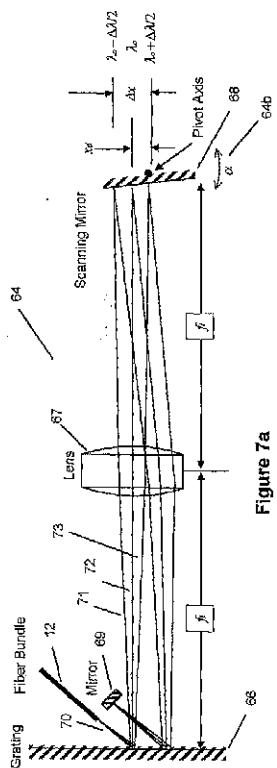
Figure 6

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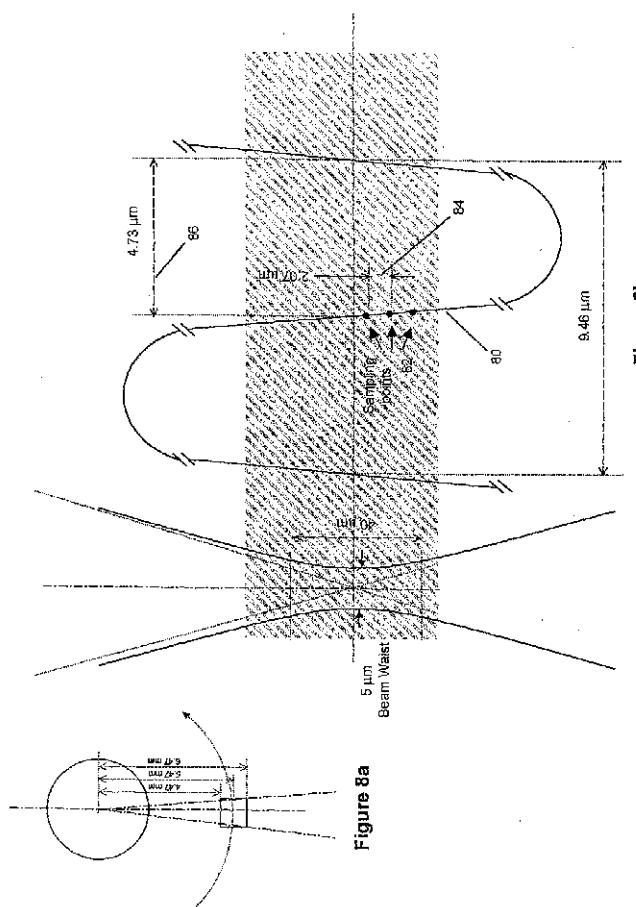


Figure 8a

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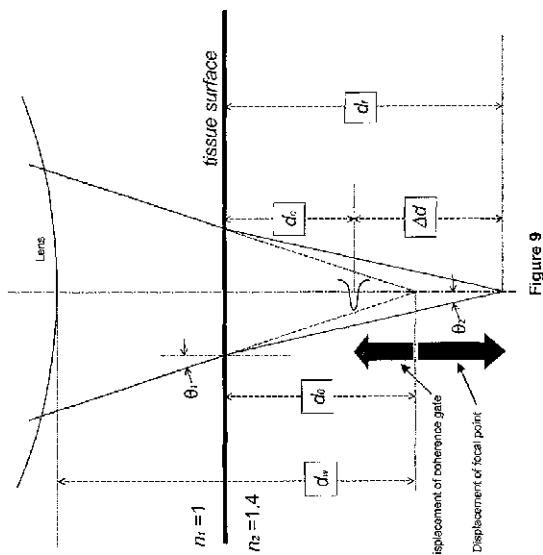


Figure 9

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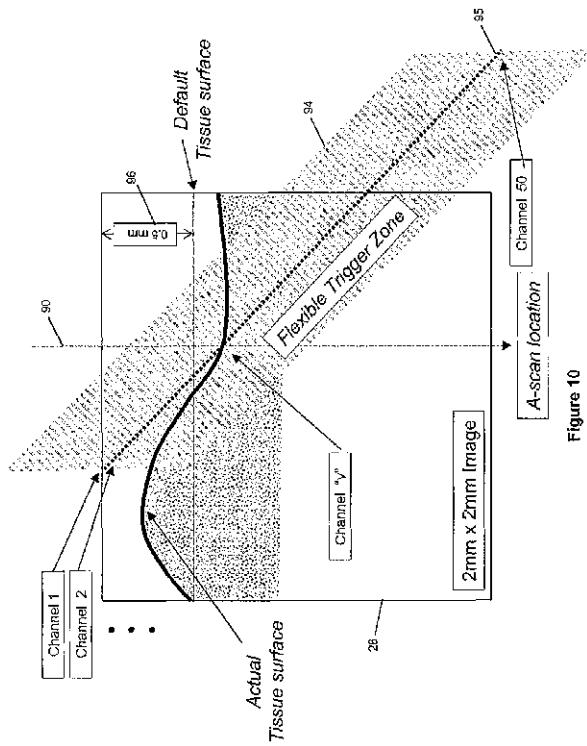


Figure 10

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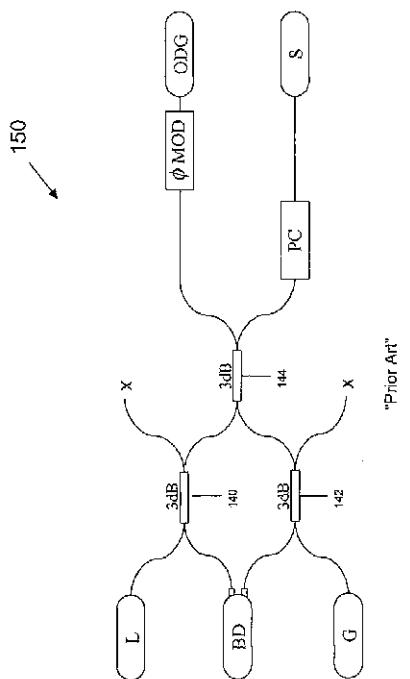


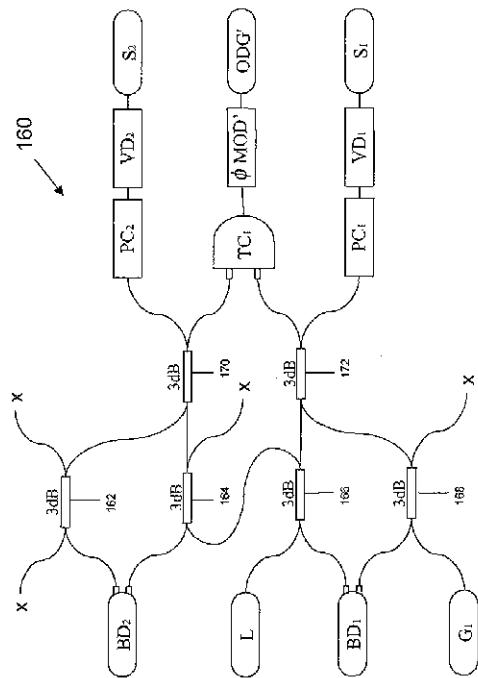
Figure 11a

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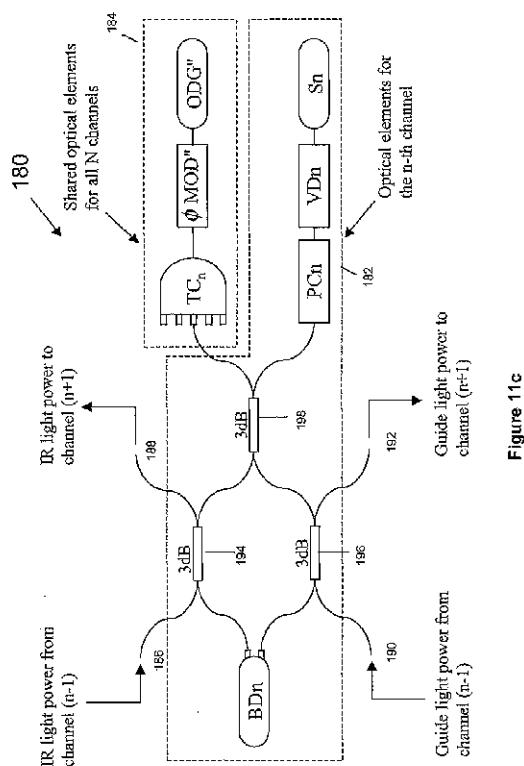
**Figure 1b**

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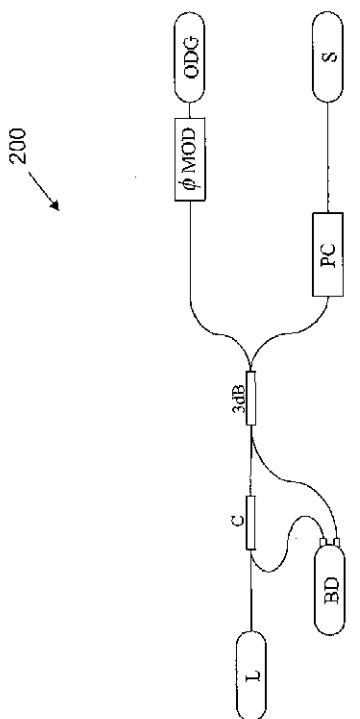
**Figure 11c**

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"Prior Art"

Figure 12a

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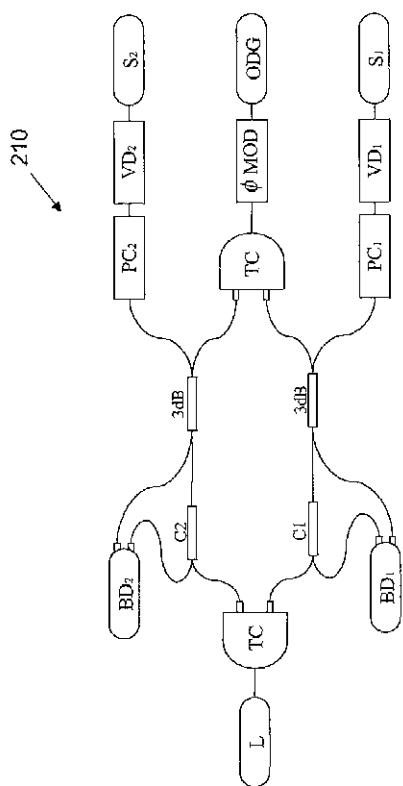


Figure 12b

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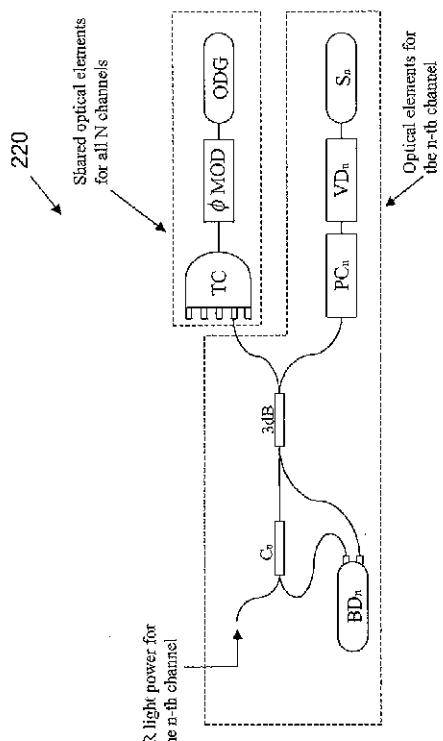


Figure 12c

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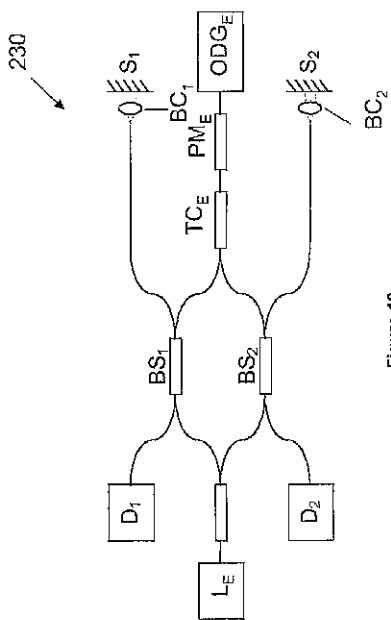


Figure 13a

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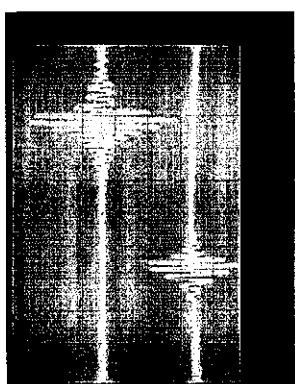


Figure 13c

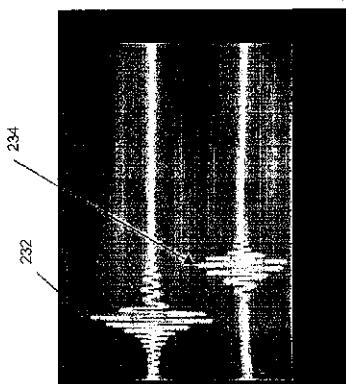


Figure 13b

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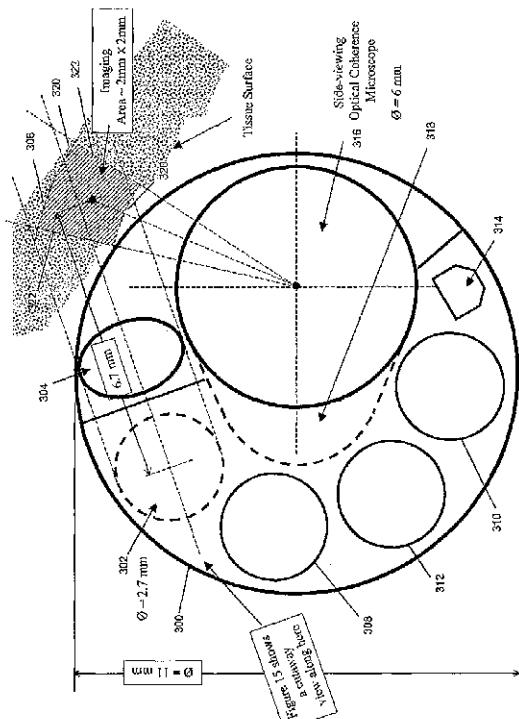


Figure 14

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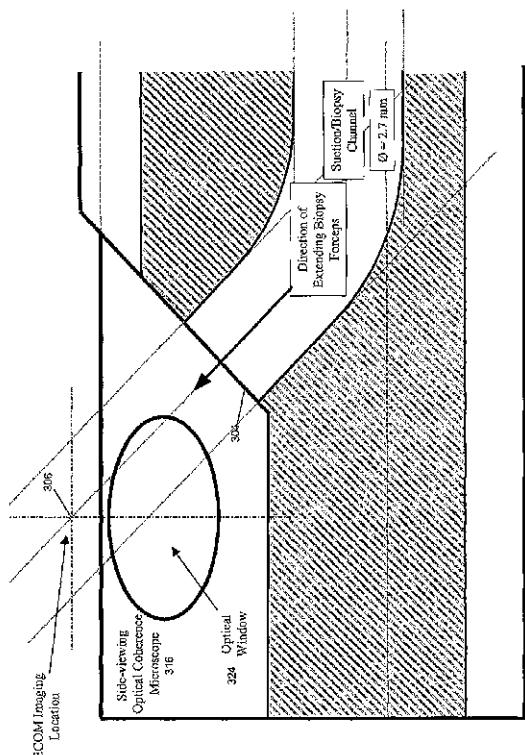


Figure 15

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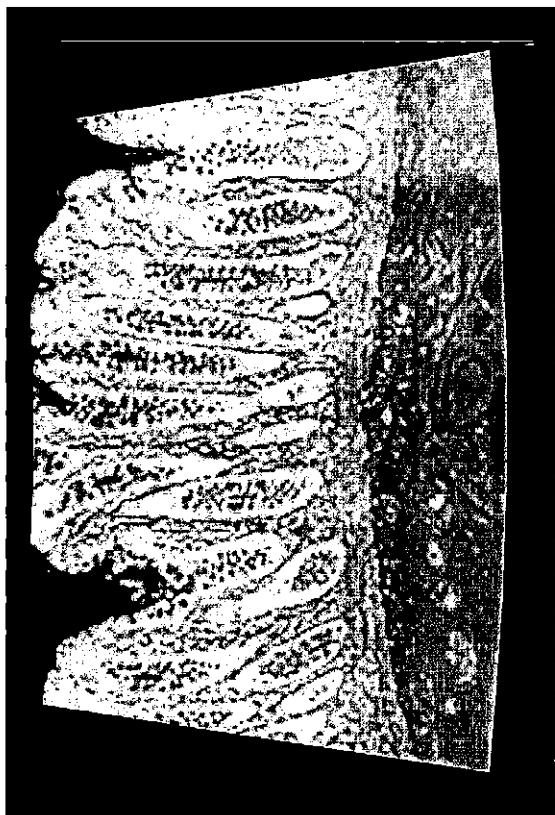


Figure 16

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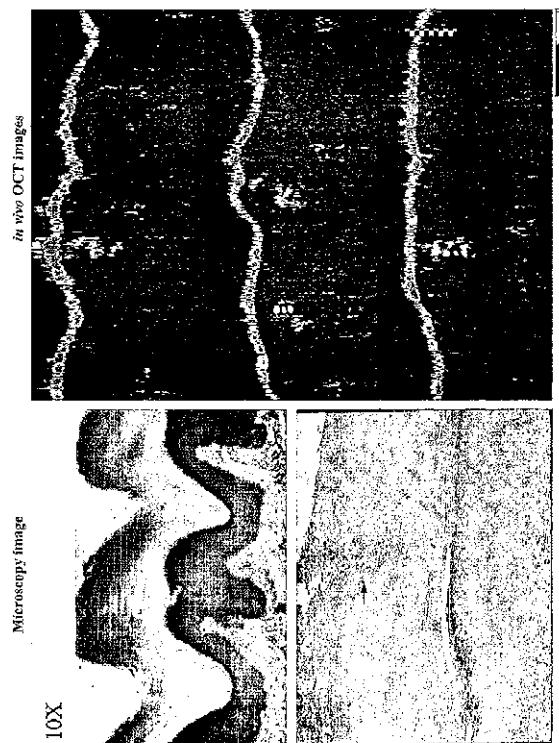


Figure 17b

Figure 17a

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## 【国際公開パンフレット(コレクトバージョン)】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number  
WO 02/004929 A3

(51) International Patent Classification: G01N 21/47 Ho, Kwan (CA/CA); 187 Spadina Road, Richmond Hill, Ontario L4B 3C5 (CA).

(21) International Application Number: PCT/CA01/00992

(22) International Filing Date: 10 July 2001 (10.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/217,090 10 July 2000 (10.07.2000) US

(71) Applicant (for all designated States except US): UNIVERSITY HEALTH NETWORK (CA/CA); Room 7-504, 610 University Avenue, Toronto, Ontario M2G 2M9 (CA).

(72) Inventors; and  
(73) Inventors/Applicants (for US only): YANG, Victor, Xiao, Dong (CA/CA); Unit - 936B, 60 Harbord Street, Toronto, Ontario M5S 3L1 (CA). VITKIN, I., Alex (CA/CA); 130 Glenlake Avenue, Toronto, Ontario M6P 1H5 (CA). WONGKEESONG, Louie (CA/US); Apartment 502, 211 2nd Street N.W., Rochester, MN 55901 (US). KATZ, Sharon (IL/CA); 77 Winifred Avenue, Toronto, Ontario M4M 2X2 (CA). GORDON, Margaret, Leslie (CA/CA); 61 Dalewood Road, Toronto, Ontario M4P 2N4 (CA). WILSON, Brian, C. (GB/CA); 85 Indian Grove, Toronto, Ontario M4R 2Y6 (CA). MOK, Alvin,

(74) Agent: BERESKIN &amp; PARR, 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, DZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KP, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), European patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IR, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

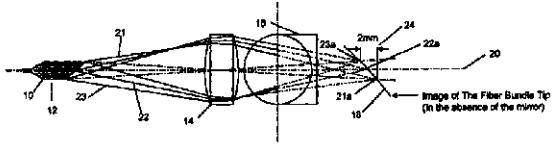
(Published:  
— with International search report

(88) Date of publication of the International search report: 26 September 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD AND APPARATUS FOR HIGH RESOLUTION COHERENT OPTICAL IMAGING

WO 02/004929 A3



(57) Abstract: A method and an apparatus for examining the sub-surface microstructure of a sample are provided. Radiation from a plurality of optical radiation sources travels along a first optical path. In the first optical path, a device focuses the optical radiation from each of the optical sources into a plurality of respective focal points along the first optical path to provide substantially continuous coverage of a selected portion of the first optical path. Then, a sample on the first optical path within the selected length extending into the sample is scanned along said selected portion of the first optical path.

## 【国際公開パンフレット（コレクトバージョン）】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

[CORRECTED VERSION]

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number  
WO 02/004929 A3

(51) International Patent Classification: G01N 21/47

(74) Agent: BERESKIN &amp; PARK, 40th Flr., 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).

(21) International Application Number: PCTCA01/00692

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, ES, FI, GR, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SU, SG, SL, SK, SI, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(22) International Filing Date: 10 July 2001 (10.07.2001)

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Hungarian patent (AM, AZ, BY, KG, KZ, MD, RU, TI, TM), European patent (AT, BE, CL, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PL, SE, TR), OAPI patent (BJ, CI, CG, CI, UM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/217,060 (10 July 2000 / 10.07.2000) US

(72) Inventors and  
with international search report

(75) Inventors/Applicants (for US only): VANG, Victor

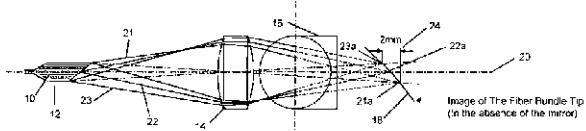
(88) Date of publication of the international search report:  
Xiao, Dong [CA/CA]; Unit 1760B, 60 Hubbard Street,  
Toronto, Ontario M5S 3L1 (CA); VITKIN, I., Alex  
[CA/CA]; 130 Glenlake Avenue, Toronto, Ontario M6P  
1R5 (CA); WONG-KEESONG, Louise [CA/US]; Apartment  
502, 211 2nd Street N.W., Rochester, MN 55901  
(US); KATZ, Sharon [CA/CA]; 77 Winifred Avenue,  
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Leslie [CA/CA]; 61 Dalewood Road, Toronto, Ontario  
M4P 2N4 (CA); WILSON, Brian C. [GB/CA]; 85 Indian  
Grove, Tooting, London SWR 2Y6 (CA); MOK, Alvin  
Ho, Kwun [CA/CA]; 187 Sydenham Road, Richmond Hill,  
Ontario L4B 3C5 (CA).(48) Date of publication of this corrected version:  
26 September 2002(49) Date of publication of this corrected version:  
7 November 2002(50) Information about Correction:  
see PCT Gazette No. 35/2002 of 7 November 2002, Section II

(51) For two-letter codes and other abbreviations, refer to the "Guide

(52) to the "Guide to the Patent Cooperation Treaty" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 02/004929 A3



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**Title: METHOD AND APPARATUS FOR HIGH RESOLUTION  
COHERENT OPTICAL IMAGING**

**FIELD OF THE INVENTION**

5 This invention relates to both a method and an apparatus for high-resolution optical imaging. More particularly, this invention is concerned with providing high-resolution imaging suitable for incorporation into an endoscope.

10 **BACKGROUND OF THE INVENTION**

Modern medical imaging techniques have important applications in health care. Modalities such as X-ray computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound imaging are the main tomographic techniques available in most modern medical centers. Visible-light endoscopy is another major imaging modality which is used extensively in procedures like bronchoscopy or colonoscopy. Each of these techniques employs different physical principles and measures different properties of the biological tissue under study with different resolution. Further, they can commonly be performed *in-vivo*. A third type of imaging, 20 optical microscopy, is still utilized widely in clinical medicine. However, optical microscopy is currently limited to detailed examination of excised or resected specimens and is not used *in-vivo*. In many circumstances, the superior contrast and resolution afforded by optical microscopy is such that physical biopsy followed by optical microscopic histology is considered the gold standard for diagnosis.

25 , Combinations of these techniques, such as using a low-resolution tomographic modality along with high-resolution imaging, biopsies or interventional procedures are constantly being studied and evaluated. Evaluation of these techniques is based on technological feasibility, clinical benefit and cost.

30 Optical Coherence Tomography (OCT) is a relatively new imaging technique based on the low-coherence property of electromagnetic radiation that enables high-resolution depth profilometry in a turbid, highly scattering

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media such as biological tissue. Its use in biomedical imaging is currently being investigated in several research and industrial laboratories. The main advantage of OCT lies in its ability to localize the depth of reflection from a sub-surface site in tissue. This localization is essentially determined by the coherence properties of the light source used and can be as low as 2 to 20  $\mu\text{m}$  for selected near-IR sources (e.g. lasers or amplified spontaneous emission devices). This gives a measure of the depth resolution attainable with OCT. Independently of the coherence characteristics, the lateral resolution is determined by the beam cross-section at the depth of imaging and by the lateral spacing of the acquired data. Typical values for lateral spacing in the literature are in the 5 to 30  $\mu\text{m}$  range. The price to be paid for this remarkable cross-sectional imaging ability in intact turbid tissue is the limited imaging depth since, due to multiple scattering and absorption, both coherence and penetration of light are degraded resulting in OCT imaging depths of approximately 2 to 3 mm.

Most current implementations of OCT are based on Michelson interferometry with a 50/50 beam splitter directing the incident coherent light beam into a reference path containing a mirror (i.e. a reference arm) and a sample path containing the interrogated sample (i.e. a sample arm). Both free-space optic and fiber-optic implementations of this scheme are currently used. Reflected beams from the mirror in the reference arm and from the tissue in the sample arm are recombined in the same splitter and half of the resultant light energy impinges on a detector. Incoherent superposition of the two light fluxes typically occurs except when the optical path lengths of the two beams are matched to within the coherence length of the source. Within this limited distance, the coherent superposition of the two light fluxes yields an interference pattern with a fringe magnitude that is proportional to the reflectivity of the tissue at that particular depth. Depth profiling of the sample is then achieved by scanning the reference arm length or more correctly by scanning the optical path length of the reference arm by using a time delay in the reference arm (this is equivalent to lengthening the reference arm). Various detection methods to measure and quantify these faint amplitude

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modulations amidst large background diffuse reflectance have been developed having a dynamic range of approximately 70 to 110 dB. Furthermore, lateral translation of the beam and axial motion of the reference mirror enables one to construct a two-dimensional reflectivity picture over a desired field of view. Means of improving the final image quality, such as performing image processing through de-convolution, have also been investigated.

The foregoing is a brief description of conventional reflectivity OCT imaging. Other variations include, for example, flow (Doppler) imaging and polarization imaging (albeit at the expense of additional complexity of the OCT optics and/or signal processing techniques). Images from these additional techniques are usually obtained in conjunction with images from conventional OCT so some image overlay or fusion is possible. Upon further technological development and/or clinical implementation, may add sufficient information content to increase the clinical utility of OCT in medicine.

However, many OCT designs and approaches that have been successfully implemented in tabletop research systems are not directly suitable for *in-vivo* imaging such as in gastroenterologic or bronchoscopic endoscopy. Instead, they may be more suitable for dermatological, ophthalmologic and dental applications. In contrast, *in-vivo* OCT imaging must address the issues of speed, resolution, contrast, penetration and instrument size. Images must be obtained sufficiently quickly to negate the effects of patient motion while still achieving suitable axial and lateral resolution, and maintaining an instrument size which is small enough to be endoscopically useful. Powerful near-IR sources, fast means of altering the reference arm length and custom-designed distal optical devices have been successfully developed to overcome the difficult challenges posed by *in-vivo* endoscopy.

The latest OCT technology employs a single-mode optical fiber with distal side-viewing optics introduced into the accessory channel of a conventional white-light endoscope. To build-up an image, the viewing direction of the OCT fiber is either linearly scanned to and fro over an approximate 2 mm distance, or is rotated via a flexible guide-wire or

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interlocking gear mechanism at several revolutions per second. Simultaneous with this translation or rotation, the reference arm length outside the endoscope is rapidly varied via an optical phase delay to generate depth scans (i.e. A-scans). Currently, these OCT systems operate at frame rates up to conventional video rates but more typically at 4 to 8 frames per second, with a frame presenting a fully circumferential view to a depth of 2 to 3 mm. The resultant resolution values are approximately 5 to 25  $\mu\text{m}$  in the depth (axial) direction and approximately 20 to 40  $\mu\text{m}$  in the lateral direction. As well, the lateral resolution generally degrades with an increase in distance from the fiber tip of the OCT device due to geometric divergence. These OCT systems have a dynamic range which is somewhat lower than that of corresponding *ex-vivo* systems due to increased noise levels and faster imaging speeds.

Based on the latest OCT technology, it is questionable whether coherent *in-vivo* OCT systems are adequate for successful clinical imaging. The images are certainly useful, but substantial improvement is required if the elusive goal of "optical biopsy" is to be realized. For example axial and lateral resolution can be improved. While the improvement in the former usually involves the use of better low-coherence sources (i.e. CW and pulsed sources), the issue of sub-optimal and depth-varying lateral resolution is more difficult to address. In *ex-vivo* systems, with its relaxed constraints of speed and physical size, lateral resolution is improved by focusing the beam to a few microns with a high-NA (numerical aperture) objective lens. In contrast to conventional OCT scanning, the imaging can now be performed in the lateral (*en face*) direction with a pre-selected depth with small oscillations in path length difference, followed by a small depth increment as necessary. The high-NA objective lens is often coupled to tissue via a refractive-index matching liquid. The general approach of using OCT with a high-NA distal optic lens is known as Optical Coherence Microscopy (OCM). However, the improved lateral resolution at the beam waist location comes at the expense of lateral blurring at other depths because the highly focused beam has a very shallow depth of field. Thus,

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the lens-to-surface distance must be varied to focus to different depths. In addition, a dynamic tracking scheme is needed to keep the location of the coherence gate (within which coherent interference between the optical beams from the sample arm and the reference arm is possible) and the beam waist at the same depth. These techniques for lateral resolution improvement have not been attempted during *in-vivo* endoscopy because of size and speed requirements.

#### **SUMMARY OF THE INVENTION**

10 The present invention is based on the concept of providing an endoscopic optical coherence tomography (OCT) device with microscopic resolution which will hereinafter be referred to as an endomicroscope. After reviewing possible clinical applications of the endomicroscope, the following parameters and features were identified since it is difficult to achieve these 15 parameters and features simultaneously with current *in vivo* OCT systems.

##### **1. High Resolution**

In order to achieve cellular and sub-cellular resolution, an 20 endomicroscope should preferably resolve features smaller than 5  $\mu\text{m}$  both in the axial and lateral directions. In contrast to most existing *in vivo* OCT systems, the lateral resolution must not degrade substantially with the depth 25 of the tissue being imaged due to geometric divergence.

##### **2. Large field of view**

An appropriate field of view of the endomicroscope is approximately  $2 \times 2$  mm in the axial and lateral directions of the optical axis. This field of view is considered to be adequate for clinical applications. In order to achieve a 5  $\mu\text{m}$  resolution in both the axial and lateral directions throughout the entire image, more than 800 A-scans (i.e. depth scans) have 30 to be performed for each frame. The resultant image will contain more than 640,000 pixels. This is several orders of magnitude higher than existing *in vivo* OCT systems.

3. Small size of endoscope tip

Most of the existing *in vivo* OCT systems are designed around the constraints of the instrument channel of existing endoscopes. As a result, 5 the outer diameter of these systems is restricted to approximately 2 to 3 mm which limits the numerical aperture of the imaging system. This makes it difficult to obtain high lateral resolution under *in vivo* conditions. These constraints may be technically unnecessary and limit one from fully 10 exploiting the benefit of OCT/OCM in the clinical applications under consideration. Accordingly, a larger outer diameter, such as 3 mm or more, for example, may be used for the endoscope as well as a length of less than 20 mm for the rigid tip.

4. High imaging speed

15 Since the endomicroscope will be used to image a large area at high resolution under *in vivo* conditions, motion artifacts must be considered because of tissue motion due to physiological motion. These motion artifacts should be eliminated to ensure good image quality. Accordingly, the endomicroscope should preferably be able to acquire a single frame 20 image within 12.6 ms given a typical physiological motion speed of 5 mm/s. This results in 63,000 A-scans per second. This imaging speed is more than one order of magnitude higher than that of current *in vivo* OCT systems.

5. Integration with currently available endoscopic imaging procedures

25 In order to improve clinical usefulness, conventional white light imaging should preferably be integrated into the endomicroscope. In addition, instrument channels should be preferably designed so that an excisional biopsy could be performed under the guidance of the endomicroscope. As well, instrument channels for water and air delivery 30 may be preferably made available.

The advanced requirements for an endomicroscope outlined above are not compatible with existing OCT/OCM designs. For instance, if

an outer diameter of 6 mm is allowed for the endomicroscope and a distal optical design is used based on a single rotating fiber as described by Tearney, G.J., Brezinski, M.E., Bouma, B.E., Boppart, S.A., Pitris, C., Southern, J.F., and Fujimoto, J.G. ("In vivo Endoscopic Optical Biopsy with Optical Coherence Tomography", *Science*, **276**: 2037-2039, 27 June 1997), then although the 5  $\mu\text{m}$  lateral resolution can be achieved at a single specific depth within the tissue in any one scan, such lateral resolution will degrade due to beam divergence at other depths. In addition, since a high NA system will be required to produce the requisite small beam waist size, the coherence gate and the focal point will not stay together in depth over a substantial (e.g. 2 mm) distance unless some dynamic compensation is implemented as described by Schmitt, J.M., Lee, S.L., and Yung, K.M ("An Optical Coherence Microscope with Enhanced Resolving Power in Thick Tissue", *Optics Communications*, **142**: 203-207, 1997). Therefore, in order to achieve some of the aforementioned requirements of the endomicroscope, dynamic focusing (changing the probe/tissue distance) and dynamic compensation (changing the path length difference) must be used. However, these focusing and compensation techniques complicate the practical realization of the device and may make it more difficult to satisfy the high imaging speed requirement. If one tries to first satisfy the imaging speed, as described by Rollins, A.M., Kulkarni, M.D., Yazdanfar, S., Ung-arunyawee, R., and Izatt, J.A. ("In vivo Video Rate Optical Coherence Tomography", *Optics Express*, Vol. 3 No. 6: 219-229, 14 September 1998), then image resolution, particularly lateral resolution, is degraded to an extent that the clinical utility of the device is compromised.

The present invention provides an endomicroscope with multiple fibers (i.e. channels) employing OCT to allow for different parts of the image to be scanned in parallel, instead of in series as is currently implemented in existing *in vivo* or *ex vivo* OCT/OCM systems. Using multiple parallel channels focused to different depths in the tissue, with each channel collecting high-resolution OCT data only across a very small axial range allows for a series of tight focal points to be achieved throughout the entire

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field of view without dynamic focusing or dynamic compensation. This greatly simplifies the design of the device which may now use mostly fixed optical components, and may facilitate high-speed operation. In addition, the intrinsically miniature dimension of the fiber optic based OCT technique 5 makes the multichannel concept possible to implement in a flexible endoscopic device while the proximal part of the endoscope, which is outside of the patient, allows room for sources, detectors, and other equipment.

In accordance with a first aspect of the present invention, there is 10 an apparatus for optical examination of a sample, the apparatus comprising: an optical source means for providing a plurality of separate optical radiation sources;

a first optical path extending from the source means; and, 15 a focusing means in the first optical path for focusing optical radiation from the optical radiation sources into a plurality of respective focal points located on a surface within the first optical path to provide substantially continuous coverage of a selected portion of the first optical path, whereby, in use, a sample can be located at least partially within the selected portion, thereby permitting simultaneous scanning of a plurality of 20 points within the sample.

In accordance with a second aspect of the present invention, an N channel apparatus for optical examination of a sample, wherein the N channel apparatus comprises a plurality of optical networks and a reference arm, each optical network providing one channel for the N channel 25 apparatus and sharing the reference arm.

In accordance with another aspect of the present invention, there is provided a method for optical examination of a sample, the method comprising:

- (a) providing radiation from a plurality of separate optical 30 radiation sources, along a first optical path;
- (b) providing focusing means in the first optical path;
- (c) focusing the optical radiation from the optical sources into a plurality of respective focal points along a surface within the first optical

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- path to provide substantially continuous coverage of a selected portion of the first optical path; and
- (d) providing a sample located at least partially within the first optical path; and,
  - 5 (e) simultaneously scanning a plurality of points within the sample.

It is to be appreciated that a sample, for use with the present invention, may comprise any biological tissue or other suitable material.

Further objects and advantages of the invention will appear from 10 the following description, taken together with the accompanying drawings.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

For a better understanding of the present invention and to demonstrate how it may be carried into effect, reference will now be made, 15 by way of example, to the accompanying drawings which show a preferred embodiment of the present invention and in which:

Figure 1a is a top view of the tip of an apparatus in accordance with the present invention showing optical paths and ignoring the refraction effects of an air-tissue interface;

20 Figure 1b is a side view of the tip of an apparatus in accordance with the present invention showing optical paths and ignoring the refraction effects of an air-tissue interface;

Figure 1c is an end view of the tip of an apparatus in accordance with the present invention showing optical paths and ignoring the refraction effects of an air-tissue interface;

25 Figure 1d is an alternate embodiment of the tip of the apparatus of Figure 1a showing optical paths and ignoring the refraction effects of an air-tissue interface;

Figure 2a shows the fiber bundle tip of Figure 1;

30 Figure 2b is a top view of an enlarged section of the fiber bundle tip;

Figure 2c is an end view of an enlarged section of the fiber bundle tip;

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- Figure 3a illustrates the focal points of three of the imaging fibers of the fiber bundle tip of Figure 1;
- Figure 3b is a magnified view of the focal points of Figure 3a showing details of the focal points at different depths;
- 5 Figure 4a is a schematic indicating different directions for directing the optical beams from the fiber bundle tip of Figure 1;
- Figures 4b and 4c are top and end views of optical beams in directions A and C of Figure 4a;
- 10 Figures 4d and 4e are top and side views of optical beams directed in directions B and D of Figure 4a;
- Figure 4f shows a perspective view of the optical beams in the directions B and D;
- Figure 5a is a beam spot diagram of a 5 channel fiber bundle tip showing electric field strength distribution near multiple focal zones;
- 15 Figure 5b is a beam spot diagram of 5 central channels of a 15 channel fiber bundle tip showing electric field strength distribution near multiple focal zones;
- Figure 5c is a graph of beam spot diameter versus focal zone distance for the fiber bundle tip of Figure 5a;
- 20 Figure 5d is a graph of beam spot diameter versus focal zone distance for the fiber bundle tip of Figure 5b;
- Figure 6 is a schematic layout of an apparatus in accordance with the present invention;
- Figures 7a is a top view of an optical delay generator used in the 25 apparatus of the present invention;
- Figure 7b is a front view of a scanning mirror used in the optical delay generator of Figure 7a.
- Figure 8a is an end view of the mirror and the focal points from three of the imaging fibers of the fiber bundle tip of Figure 1a;
- 30 Figure 8b shows a combined A-scan and a two-dimensional brightness-mode (B-mode) scan path for light radiated from a single imaging fiber of the present invention;

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Figure 9 is a diagram illustrating mismatch between the coherence gate and the focal point due to the air-tissue interface for light radiating from a single imaging fiber of the present invention;

5 Figure 10 is a diagram illustrating flexible triggering of the apparatus of the present invention to accommodate the mismatch shown in Figure 9;

Figure 11a is a schematic diagram of a Prior Art single channel Optical Coherence Tomography device;

10 Figure 11b is a schematic diagram of a two channel Optical Coherence Tomography device;

Figure 11c is a schematic diagram of an optical network that could be used to construct an N-channel Optical Coherence Tomography device;

15 Figure 12a is a schematic diagram of a single channel Optical Coherence Tomography device with an optical circulator;

Figure 12b is a schematic diagram of a two channel Optical Coherence Tomography device employing optical circulators;

20 Figure 12c is a schematic diagram of an optical network that could be used to construct an N channel Optical Coherence Tomography device employing an optical circulator;

Figure 13a is a schematic of an experimental setup used to investigate cross-talk between optical channels sharing components;

25 Figure 13b is an experimental result from experimentation on the setup of Figure 13a;

Figure 13c is another experimental result from experimentation on the setup of Figure 13a;

Figure 14 is an end view of a GI endoscopic coherent optical microscope in accordance with the present invention;

30 Figure 15 is a cutaway side view of the GI endoscopic coherent optical microscope of Figure 14 showing a biopsy channel;

Figure 16 is a simulated image of a human colon epithelium that is expected to be obtained with the apparatus of the present invention;

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Figure 17a has two panels which each show a microscopy image of sweat ducts in the human skin; and,

Figure 17 b has three panels which each show an *in vivo* OCT image of sweat ducts in the human skin.

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#### DETAILED DESCRIPTION OF THE INVENTION

In the following description, various specific dimensions and other parameters are mentioned such as the wavelength used by the imaging source and the physical dimensions of the optical components used in the 10 apparatus. It is to be appreciated that this is for exemplary purposes only and does not limit this invention. Specific parameters, dimensions and the like may be chosen depending on an intended application of the invention.

Referring to Figure 1, the present invention provides an apparatus comprising an endoscopic coherent optical microscope having 15 multiple single mode fibers 10, a fiber bundle tip 12, a focusing lens 14 and a mirror 16. The multiple single mode fibers 10 and the focusing lens 14 are stationary while the mirror 16 is rotatable. Accordingly, the mirror 16 is mounted for rotation in known manner. Details of the rotating mechanism for the mirror 16 are not described further and can be conventional. Multiple 20 single mode fibers 10 (of which there may be approximately 50 fibers) form an array at the fiber bundle tip 12. This array is cleaved and arranged in a "staircase" pattern as shown in Figure 2. Radiated light from the fiber bundle tip 12 is focused by the focusing lens 14 and reflected by the mirror 16. The focusing lens 14 may have a diameter of 5 mm (i.e.  $\phi = 5$  mm) and 25 a focal length of 5 mm (i.e.  $f = 5$  mm). The mirror 16 may have a diameter of 5 mm and a front face that is cleaved at 45°. A magnified image of the focal points of the fiber bundle tip 12 is shown in Figure 3.

Figure 1a shows three beams 21, 22 and 23 from three exemplary fibers arbitrarily chosen from the multiple single mode fibers 10. 30 Due to the staggered or staircase nature of the multiple single mode fibers 10 (see Figure 2), each of the beams 21, 22 and 23 originates from a different point and consequently is brought into focus, by the focusing lens

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14, at a different point 21a, 22a and 23a on a surface 18 when the mirror 16 is not used. It will be appreciated that a similar effect is achieved for all of the multiple single mode fibers 10 of the fiber bundle tip 12 to produce beams focused to different points on the surface 18. As indicated at 24 (and 5 as shown in Figure 3), if the multiple single mode fibers 10 comprise 50 optical fibers, each being focused within a short range of approximately 40 microns and having their ends staggered to space the focal points apart by 40 microns (as measured along axis 20 of the focusing lens 14), a total range or depth of 2 mm is covered. The axis 20 for the focusing lens 14 is 10 part of a first optical path.

With the mirror 16 present, the optical beams 21, 22 and 23 are focused as shown in Figures 1b and 1c. Thus, three focal points 21b, 22b and 23b are spaced apart in a vertical or depth direction along axis 26 which forms an extension of the first optical path. As the view of Figure 1c shows, the three focal points 21b, 22b and 23b are also spaced apart in the circumferential direction (i.e. they are spaced apart laterally) relative to the motion of the mirror 16. The three focal points 21b, 22b and 23b fall on a surface 27 to facilitate imaging of a selected portion of the first optical path. The surface 27 may be a complex surface or a planar surface. If multiple 20 single mode fibers 10 comprises 50 individual fibers, then the focal points of all the individual fibers from the fiber bundle tip 12 would be spaced apart correspondingly. Alternatively, the reflected focal points 21b, 22b and 23b do not necessarily have to be perpendicular to the axis 20 but may be at a large angle to the axis 20.

25 Rotation of the mirror 16 results in motion of the surface 27. This enables a two-dimensional B-scan image 30 to be obtained, as shown in Figure 1c, covering a scan area 28 which has a square shape with preferable dimensions of 2 mm x 2 mm. The B-scan image 30 indicates an exemplary view that may be obtained for the scan area 28.

30 Redesigning the multiple single mode fibers 10, for example, by changing the diameter of the core and cladding of the multiple single mode fibers 10, results in variations on the surface 27. Furthermore, optical wave

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guide wafers may also be used in the place of the multiple single mode fibers 10.

In an alternative embodiment, the mirror 16 may be replaced by a mirror 16' that moves linearly in combination with the focusing lens 14 and the fiber bundle tip 12 as shown in Figure 1d. The linear translation may preferably incorporate a reciprocal motion. In terms of mechanics, the fiber bundle tip 12, depicted in Figure 1a, utilizes a radial scanning motion. The radial scanning motion is well suited for scanning organs having larger diameters, such as the esophagus or the large intestine. However, due to the complex driving mechanism needed for radial scanning, the diameter of the fiber bundle tip 12 will not allow for endomicroscopy in organs having small inner diameters such as blood vessels. Therefore, the alternative embodiment shown in Figure 1d may be used which comprises a similar fiber bundle tip 12' that is adapted to perform linear translational scanning instead of radial scanning.

As shown in Figure 1d, the main differences between the two methods of scanning are that the mirror 16' will not be rotating and the entire fiber bundle tip 12' needs to be translated along its horizontal axis in preferably a reciprocal motion over a range of 4 mm for example. Mechanically, the linear translational scanning motion is less complicated than the radial scanning motion. In addition, linear translational scanning is better suited for endomicroscopy in organs having a small inner diameter such as blood vessels. However, for some larger organs, such as the large intestine, linear translational scanning is not as well suited due to positioning difficulties.

In a further alternative embodiment, both of the scanning motions may be combined to produce an endomicroscopy device having helical scanning. The helical scanning motion would comprise the rotational movement of the mirror 16 in combination with the linear translation of the mirror 16, the focusing lens 14 and the fiber bundle tip 16. Such an endomicroscopy device may be more suitable for imaging certain types of organs such as the human large intestine. The helical scanning

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endomicroscopy device may be implemented by linearly translating the apparatus shown in Figure 1a.

In yet another alternative embodiment, the fiber bundle tip 12 may be altered to employ a Micromachined Electro-Mechanical System (MEMS) driving mechanism. Since the aforementioned embodiments require some form of motion for the mirror 16, all embodiments require mechanical driving mechanisms. Accordingly, a motor is situated outside of the endoscope and a mechanical drive-train mechanism or wire is placed along the entire length of the endoscope. However, the multi-channel fiber optical design is not restricted to such mechanical driving means. In fact, due to the extremely small spatial resolutions realizable by the multi-channel system, adverse effects, such as vibration induced polarization dependence, from the mechanical drive means, may limit the full potential of the present invention if a mechanical drive means is utilized. Therefore, a MEMS electrical driving mechanism may be employed where electrically-driven, micro-mechanical optical devices are used to facilitate the scanning. This implementation may potentially circumvent the adverse effects that may be caused by a mechanical driving mechanism since the MEMS implementation reduces vibrations along the axis of the device except in the vicinity of the object which is being translated such as the mirror 16. The MEMS implementation may also offer advantages in terms of miniaturization and performance.

In a further alternative embodiment, the fiber bundle tip may not require the mirror 16. The combination of the fiber bundle tip 12 and the focusing lens 14 may be pivotally attached. Accordingly, through a pivoting motion, the combination of the fiber bundle tip 12 and the focusing lens 14 may be adapted to direct a plurality of focusing points along portions of a plurality of surfaces extending into the sample to construct the B-scan image 30 of the scan area 28.

In yet another embodiment, the mirror 16 may be a surface of a prism. The rest of the apparatus would follow as previously described and shown in Figures 1a to 1d.

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It should further be understood that the optical path can be straight, bent or curved. Furthermore, the optical path may be a 3 dimensional path having a length, width and height. Depending on the scanning motion (i.e. radial, linear or helical), the orientation of the surface, upon which the focal points reside, may also vary. Furthermore, the optical path may comprise optical radiation from one optical radiation source or a plurality of optical radiation sources (i.e. a plurality of light sources or a plurality of fibers each transmitting optical radiation).

Referring now to Figures 2b and 2c, a magnified view of the fiber bundle tip 12 comprising the multiple single mode fibers 10 is shown. Each of the multiple single mode fibers 10 comprises a cladding 10a around a core 10b having diameters of, for example, 40 µm and 5 µm respectively. The ends of the multiple single mode fibers 10 may be stepped by 40 µm so that the focal points of the optical radiation through each of these fibers are spaced apart. However, a step spacing other than 40 µm may also be used.

Referring now to Figure 3, A-scans for each of the multiple single mode fibers 10, in the fiber bundle tip 12, are acquired over approximately the entire 2 mm imaging depth, but retained only over a short axial range of approximately 40 µm near the focal point of each fiber where the beam diameter is close to a minimum (indicated at 34) and does not vary substantially with axial position. This range of 40 µm, in this exemplary design, is indicated at 31. The A-scans are performed simultaneously by each of the multiple single mode fibers 10 within the fiber bundle tip 12. Effectively, the multiple A-scans cover the entire depth of 2 mm in the sample tissue at different radial directions, but for each of the multiple single mode fibers 10, only sections of the respective A-scan in a corresponding 40 µm depth-of-focus 31 are used to build up the image. As shown in the focal zone 31, each of the beams 21b, 22b and 23b show a distinct "hourglass" shape for the focal points 38, 37 and 36, in known manner. For each of the beams 21b, 22b and 23b, the far field beam spread is indicated by lines 32 and the near field beam spread is indicated by lines 34.

The purpose of rotating the mirror 16 is to create radial (i.e. lateral) scans in a direction that is perpendicular to the A-scan direction to create a B-scan image, i.e. the scan area 28 of Figure 1. The resultant radial scan pattern of the focal points of the individual fibers from the 5 multiple single mode fibers 10 is illustrated in Figure 4. It is worth noting that a continuous scan surface is only present when the cleaved face of the mirror 16 is faced substantially in the direction of locations "A" and "C", where B-scan images should be taken. At other locations on the radial scan pattern, a "dead space" between the individual A-scans is too large to allow 10 for sufficient sampling of the tissue. Therefore, the present invention comprises a sector-scan imaging device, to scan a sector substantially in the "A" or "C" locations, with a sector angle of about 20°, within which a 2 mm by 2 mm image is obtained. In this example, with the given geometry, a larger sector angle will produce "dead spaces" which are too large to form a 15 suitable cross-sectional image.

Figures 4b and 4c show beam focal points 36, 37 and 38 from both a top view and an end view respectively. As shown, and corresponding to earlier figures, the individual focal points 36, 37 and 38 are spaced apart 20 in the radial plane perpendicular to the axis 20. As Figure 4c shows, in an end view along the axis 26, the focal points 36, 37 and 38 are spaced apart in terms of depth but overlap to create a continuous scanning surface or scan area 28.

If, the cleaved face of the mirror 16 is faced substantially in the 25 direction of the locations indicated at "B" and "D", in Figure 4a, which is perpendicular to the scanning surface or scan area 28, then the patterns shown in Figure 4d (a top view of the pattern) and Figure 4e (a side view of the pattern) are obtained. Here, the focal points are indicated at 40, 41 and 42. As shown in Figure 4d, the focal points 40, 41 and 42 are each in an 30 individual plane 40', 41' and 42' which are spaced apart corresponding to the spacing of the fibers in the fiber bundle tip 12. The planes 40', 41' and 42' are perpendicular to the axis 20. In Figures 4b to 4e, arrows 44 indicate the direction of the radial scan.

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For the linearly translated system shown in Figure 1d, there are no "dead spaces" and thus linear translation can produce images suitable images approximately 2 mm by 2 mm in size.

In the exemplary design of the endomicroscopic system, the maximal speed of tissue motion, due to physiological motion, was chosen as 5 mm/s for *in vivo* imaging. A near diffraction-limited focusing lens (i.e. a lens which approximates an ideal lens by providing very small focal points) was chosen as the focusing lens 14. The near diffraction-limited focusing lens was supplied by Melles Griot Inc. In addition, each single mode fiber, from the plurality of single mode fibers 10, had a core diameter of 5 microns (i.e.  $\phi_c \approx 5 \mu\text{m}$ ) and was operated at a wavelength of 0.86  $\mu\text{m}$ . Furthermore, the design incorporates an approximate core index of  $n_c = 1.447$  and a difference in the refractive index between the core and the cladding of  $\Delta n = 0.005$ . Using these values, the NA of the fiber is then given by:

$$NA \approx n_c(2\Delta n)^{1/2} = 0.145 \quad (1)$$

and the acceptance angle,  $\theta_a$ , of the fiber is given by:

$$\theta_a = \sin^{-1}(NA) = 8.32^\circ = 0.145 \text{ rad} \quad (2)$$

The design further incorporates the concept of an ideal lens which is used to focus optical radiation, from the plurality of single mode fibers 10, at a magnification of 1 to 1 and that the far field beam divergence angle is similar to  $\theta_a$ . Then, for light beam radiation with a center wavelength  $\lambda_0$ , the beam diameter at the focal point is given by:

$$\phi_f = 2w_0 = 2 \frac{\lambda_0}{\pi\theta_a} = 3.95 \mu\text{m} \approx \phi_c \quad (3)$$

The spot diameter  $\phi_f$  is approximately equal to the core diameter ( $\phi_c = 5 \mu\text{m}$ ) which results in efficient optical coupling. The depth of focus is  $2 \frac{\pi w_0^2}{\lambda_0} = 27.2$  mm and the beam diameter at the ends of the focal zones for focal points 36, 37 and 38 is given by:

$$\phi_f' = 2\sqrt{2} w_0 = 5.59 \text{ mm} \quad (4)$$

Since the  $\phi_f$  and  $\phi_f'$  parameters are defined in terms of amplitudes, within 40  $\mu\text{m}$  of the focal point in the axial direction, the beam diameter based on

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light intensity (i.e. the square of the light amplitude) may actually be smaller than 5  $\mu\text{m}$ .

The above calculation is based on ideal optics operating on the principle optical axis. Using an off-the-shelf lens system with  $\mathcal{D} = 5 \text{ mm}$ ,  $f = 5 \text{ mm}$ , and a working distance of 8.2 mm, it has been found that the off-axis angle required to cover a 2 by 2 mm image is about 5° using commercial ray-tracing software. At approximately an 80% fill factor of the focusing lens 14, the ray-tracing results show the on-axis RMS focal point to be 5.3  $\mu\text{m}$  in radius, and the 5° off-axis RMS focal point to be 10.3  $\mu\text{m}$  in radius. A custom designed lens system should have better performance.

As illustrated in Figure 1, the working distance of the entire optical system, i.e. the distance from the focusing lens 14 to the focal point of the apparatus is determined by the focal length of the lens system, the diameter of the focusing lens 14 and the gap between the focusing lens 14 and the mirror 16. Using the off-the-shelf lens system discussed above, the working distance is about 2.35 mm. The distance from the center of the image to the rotational axis of the mirror 16 is about 5.47 mm. To obtain a 2 mm scan in the radial direction, the sector scanning angle should be approximately  $\pm 10.4^\circ$ , or about 20° in total, as determined by the geometry of the optical system.

Currently existing *in vivo* OCT systems perform radial scans at 4 to 8 revolutions per second (RPS) to yield a biologically acceptable 4 to 8 frames per second. For the design of the present embodiment, 4.4 RPS is chosen as the rotational speed. The rotational speed depends on the repetition rate of the A-scans and the number of A-scans required to obtain a 5  $\mu\text{m}$  lateral resolution. Therefore, the imaging speed of the apparatus of the present invention is 4.4 frames/s while other imaging speeds may be chosen based on different end-user applications. The imaging time for each individual frame is 12.6 ms, as determined by the rotation speed and the sector scanning angle. Therefore, for a given frame, the system is acquiring signals for 12.6 ms and the time between frames is about 215 ms during which data processing is performed. These parameters are dependent on

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the performance of the optical delay generator (which is described later) that is used in the system.

While the above calculations were made based on a light source operating at a light wavelength of 860 nm and custom made single mode fibers, implementation using a light source operating at other wavelengths, such as 1300 nm, and off-the-shelf fiber may also be possible. Figure 5a shows a beam spot diagram for a 5 channel fiber bundle tip operating at a wavelength of 1300 nm and using off-the-shelf fibers (Corning SMF-28). The fiber bundle tip has a fiber step size of 125  $\mu\text{m}$ . The light beams from these fibers, focused by a lens having a 5 mm diameter and a 4.5 mm focal length, cover a focal zone of approximately 0.65 mm. The resulting lateral imaging resolution is approximately 10  $\mu\text{m}$ . Figure 5b shows a beam spot diagram for a 15 channel fiber bundle tip operating at a wavelength of 890 nm and using custom designed fibers having a core diameter of 5  $\mu\text{m}$  and a cladding diameter of 40  $\mu\text{m}$ . This fiber bundle tip has a fiber step size of 40  $\mu\text{m}$ . The beams spots of only the central 5 channels are shown. The resulting lateral imaging resolution is approximately 5  $\mu\text{m}$  over a focal zone of approximately 0.65 mm.

Figure 5c shows beam spot diameter versus distance along the focal zone for the 5 channel fiber bundle tip of Figure 5a. Figure 5c shows that the beam spot diameter is consistently less than 15  $\mu\text{m}$  over the entire 0.65 mm focal zone. Figure 5d shows beam spot diameter versus distance along the focal zone for the 15 channel fiber bundle tip of Figure 5b. Figure 5d shows that the beam spot diameter is approximately 5  $\mu\text{m}$  over the entire 0.65 mm focal zone.

Referring now to Figure 6, the overall general layout of the basic optical elements of the apparatus of the present invention comprises a plurality of optical sources 50, a plurality of tree couplers 52, a plurality of 3 dB couplers 54, a fiber bundle tip 56, a plurality of detectors 58, a plurality of demodulators 60 and an optical delay generator 64. The plurality of optical sources 50, which may be lasers, are connected to the plurality of tree couplers 52. More than one laser may be needed to ensure that

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adequate optical radiation is provided to each of the fibers (i.e. channels) in the tip 56. Each tree coupler 52 couples a respective optical source 50 to a subset of the plurality of 3 dB couplers 54. The plurality of 3 dB couplers 54 are connected to the fiber bundle tip 56 for onward transmission of approximately half of the light radiation from the plurality of optical sources 50. The fiber bundle tip 56 includes fiber bundle tip 12 and the other optical elements of Figure 1 (i.e. the focusing lens 14 and the mirror 16). The other half of the radiation from the plurality of optical sources 50 is reflected back to detectors 58 which in turn are connected through the demodulators 60 to a computer 62 which functions to process the sampled data to generate the B-scan image 30. The optical delay generator 64 is used by the 3 dB couplers 54 to provide a delayed reflected signal to the detectors 58. The sample being investigated by the tip 56 is indicated at 65.

In the layout shown in Figure 6, 1 dB or 10 dB optical couplers and the like may be used in place of the 3 dB couplers 54. Furthermore, the intensity of the optical radiation transmitted to each of the 3 dB couplers 54, and consequently each fiber, by the tree couplers 52 need not be the same and in fact is chosen depending on whether the 3 dB coupler provides optical radiation to a fiber (i.e. channel) that facilitates a deep or shallow scan into the tissue. High intensity optical radiation is needed to scan deeply into the tissue. Accordingly, tree couplers 52 and 3 dB couplers 54 that feed optical radiation to fibers that scan deeply into the tissue are adapted to provide larger amounts of optical radiation.

Figures 7a and 7b show the optical delay generator 64 in greater detail. The optical delay generator 64, similar to those in existing *in vivo* OCT systems, is used to perform the A-scans using the coherence envelope of each individual fiber. The optical delay generator 64 comprises a grating 66, a lens 67, a scanning mirror 68 and a mirror 70. Rapid depth scanning can be achieved with the optical delay generator 64 by dispersing quasi-monochromatic light from the multiple single mode fibers 10 in the fiber bundle tip 12 onto the diffraction grating 66 and focusing the dispersed light onto the oscillating mirror 69. This has the effect of applying a linear ramp in the frequency or Fourier domain as described by G. J. Tearney,

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B.E. Bouma and J. G. Fujimoto ("High-speed phase and group delay scanning with a grating based phase control line" Nature Medicine 4(7), 861-865 (1998)). With recombination of the reflected wavelengths at the diffraction grating 66, a real space-time delay is created. The angle of the scanning mirror 68 is rapidly oscillated through several degrees of rotation creating a rapidly varying time delay in the reference arm which allows for fast, repeated depth scanning of a sample.

The optical radiation 70 from one fiber from the multiple single mode fibers 10 is shown in Figure 7a. The optical radiation 70 is dispersed into spectral components represented by spectral components 71, 72 and 73 by the grating 66. Spectral component 71 represents the lowest wavelength in the optical radiation 70; spectral component 73 represents the highest wavelength in the optical radiation 70; and spectral component 72 represents the center wavelength in the optical radiation 70. These spectral components of the optical radiation 70 are vertically aligned in the optical delay generator 64. In a similar fashion, optical radiation from other fibers from the multiple single mode fibers 10 are dispersed and vertically aligned, with a vertical spacing between the dispersed optical radiation from the different fibers. The offset of the center wavelength of the dispersed optical radiation from the pivot axis of the scanning mirror 68, for a given fiber, is represented by  $x_d$  which facilitates phase modulation of the dispersed optical radiation from each of the multiple single mode fibers 10. Alternatively, if  $x_d$  were zero then a phase modulator would be needed, for each of the single mode fibers 10, to phase modulate the optical radiation from each of the single mode fibers 10. This has the advantage of allowing for a reduction in size of the scanning mirror 68 which in turn allows for a higher frame rate to be used. Furthermore, the phase modulator is electrically controlled which allows for very stable signals are generated

Referring now to Figure 7b, the multiple single mode fibers 10 are aligned in the fiber bundle tip 12, such that dispersed optical radiation from each of the multiple single mode fibers 10 is vertically aligned on the scanning mirror 68 as rows 75, 76, 77 and 78. Alternatively, other ordered arrangements may also be used for the spectral components of the optical

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radiation from each fiber from the multiple single mode fibers 10 such as columns.

As illustrated in Figure 6, a single optical delay generator may be used to introduce delay in multiple fibers. The limiting factor in determining 5 the number of channels that may be coupled to a single optical delay generator is the physical size of the scanning mirror which is in turn limited by the resonance frequency of the optical delay generator. Commercially available resonance optical scanners can operate up to 16 kHz. Accordingly, a size of 4 mm by 5 mm may be used for the scanning mirror 10 68. Since the fiber bundle array is about 2 mm in size, it is possible to fit the entire array onto one optical delay generator. Therefore, for the embodiment of the present invention, a single optical delay generator is used having an optical scanner operating at  $f_r = 16$  kHz with an optical scan angle  $\alpha$  of  $\pm 2^\circ$ . The embodiment also incorporates a grating pitch of  $p = 15$  3.33  $\mu\text{m}$ , a center wavelength of  $\lambda_0 = 0.86 \mu\text{m}$  and a focal length of  $f_i = 21$  mm. Accordingly, the free space group path length difference  $\Delta l_g$  is given by (from Rollins et al. 1998):

$$\Delta l_g = 4\alpha(f_i \frac{\lambda_0}{p} - x_d) = 0.618 \text{ mm} \quad (5)$$

which is also 1.24 mm peak to peak. In equation 5,  $x_d = 1$  mm is the 20 displacement between the  $\lambda_0$  spectral line and the pivoting axis on the resonance mirror. The peak A-scan speed is given by:

$$V_{A\max} = 2\pi\Delta l_g f_r = 62.1 \text{ m/s} \quad (6)$$

and the A-scan speed varies according to equation 7.

$$V_A = V_{A\max} \cos(2\pi f_i t) \quad (7)$$

Choosing a source with a coherence length  $l_c$  of 5  $\mu\text{m}$  and a Gaussian 25 emission spectrum, the equivalent emission bandwidth is given by:

$$\Delta\lambda = \beta \frac{\lambda_0^2}{l_c} = 98 \text{ nm} \quad (8)$$

where  $\beta = 0.66$  for a Gaussian envelope.

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The size of the resonant mirror is determined next. For an optical delay generator with a grating having a first order diffraction, the diffraction angle is given by:

$$\theta(\lambda) = \sin^{-1}(\lambda/p) \quad (8)$$

- 5 The spread of the spectrum from  $(\lambda_0 - \Delta\lambda/2)$  to  $(\lambda_0 + \Delta\lambda/2)$  at the Fourier plane of the lens is given by:

$$\Delta\lambda = 2f_i[\theta(\lambda_0 + \Delta\lambda/2) - \theta(\lambda_0 - \Delta\lambda/2)] = 1.3 \text{ mm} \quad (10)$$

Since the mirror width is 4 mm, one can fit the spectrum on one side of the resonant mirror with the displacement  $x_d$  having a value of approximately 1 mm. This is illustrated in Figures 7a and 7b. The carrier frequency of an individual channel of the system is given by (Rollins et al. 1998):

$$f_c = (4x_d\alpha 2\pi f_i/\lambda_0)\cos(2\pi f_i t) \quad (11)$$

which is 16.3 MHz at the maximum.

- 15 The bandwidth of the interferogram (i.e. the interference fringe pattern) is given by:

$$\Delta f = \frac{\Delta\lambda}{\lambda_0^2} 4\pi\alpha f_i \cdot 2(f_i \lambda_0 / p - x_d) \cos(2\pi f_i t) \quad (12)$$

which is 8.4 MHz at the maximum.

Since  $f_c(t) > \Delta f(t)$ , proper demodulation can be performed by conventional rectifying and low-pass filtering, although a sharp frequency cut-off is needed. It is preferable to set up the individual channels of the system such that  $D_A = 40 \mu\text{m}$  (the depth of the A-scan performed by a single channel) coincides with the maximum carrier frequency, so that the variation in carrier frequency over  $D_A$  is minimized. The carrier frequency varies sinusoidally in time given by:

$$\Delta f_c = f_c \{1 - \cos[\sin^{-1}(D_A/\Delta l_g)]\} = 34 \text{ kHz} \quad (13)$$

which is about 0.2% of  $f_c$ .

At other locations, the signal can still be properly demodulated, but the variation in carrier frequency will be larger. The demodulators 60 may incorporate an analog high-speed rectifier and a 10-pole low-pass filter to demodulate the signal. Effectively, the signal is frequency down-shifted

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such that the signal is centered at DC and has a bandwidth of  $\Delta f$ . The demodulated envelope signal is then digitized at an appropriate sampling rate. Current existing data acquisition (DAQ) cards operate at 30 MegaSamples per second (MS/s) with an SNR of about 60 dB. Choosing a Gaussian shape for the interferogram spectrum with  $\Delta f = 8.4$  MHz, the 60 dB point is at about 14.5 MHz. Accordingly, the Nyquist rate for digitizing such a signal is approximately 29 MS/s. Therefore, current existing DAQ cards will be able to digitize the envelope signal without aliasing.

Given a sampling rate of 30 MS/s for digitizing the envelope signal at the maximum carrier frequency, the spatial sampling interval in the axial direction is:  $\Delta_{axial} = V_{Axial}/S = 2.07 \mu\text{m}$ . As shown in Figure 8, a scan path 80 is indicated showing A-scans alternately going up and down through the sample. Sampling points are indicated at 82. The axial spacing of 2.07  $\mu\text{m}$  is indicated at 84. The spatial sampling interval in the lateral direction is determined by the lateral or B-scan velocity and the resonant frequency of the optical scanner in the optical delay generator 64. At the center of the image, where the radial distance  $r$  is 5.47 mm from the rotational axis of the mirror, the radial sampling interval is given by:

$$\Delta_{radial} = \frac{V_{radial}}{2f_r} = \frac{2\pi\Omega^2}{2f_r} = 4.73 \mu\text{m} \quad (14)$$

This interval is indicated at 86 in Figure 8. For the fiber scanning the shallowest depth, the spatial lateral sampling interval is 3.86  $\mu\text{m}$  and for the deepest channel it is 5.59  $\mu\text{m}$ . Therefore, the pixel size at the center of the image is 2.07 by 4.73  $\mu\text{m}$  in the axial and lateral direction respectively. The lateral pixel size varies across the depth of the image from 3.86 to 5.59  $\mu\text{m}$ . By varying the rotational speed of the mirror 16, the lateral sampling interval can be changed, at the expense of frame rate. If a higher resonance frequency optical scanner is used, the sampling interval may also be reduced.

For a pulsed optical source (e.g. a 15 to 20 fs pulsed laser emitting light with a wavelength of 860 nm), the coherence length will be approximately 4.5 to 6  $\mu\text{m}$ . Since the spatial sampling interval in the axial

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direction is about 2  $\mu\text{m}$ , which is smaller than half of the coherence length, the image is reasonably sampled in the axial direction. Using a near diffraction-limited focusing lens as the focusing lens 14, the beam spot size should be about 5  $\mu\text{m}$ . Since the spatial sampling interval in the lateral direction varies from 3.86 to 5.59  $\mu\text{m}$ , the image is slightly under sampled, given that the beam waist size is about 5  $\mu\text{m}$ . However, the spatial sampling interval is not equivalent to the final image resolution, which is also influenced by local contrast and noise levels. Local contrast is the difference in reflectivity between two points in the sample that show up as adjacent pixels in the image. If the two points have similar reflectivity, i.e. low local contrast, it will be difficult to resolve these points.

10 Imaging speed should be fast enough to reduce motion blurring. Given that the target speed (i.e. tissue motion) is typically 5 mm/sec, then within a frame time (an elapsed time of 12.6 ms), the target can move up to 15 63  $\mu\text{m}$  in a particular direction which is much larger than the designed 5  $\mu\text{m}$  resolution. In the present embodiment, the A-scan is performed simultaneously in all channels such that one line of the image is formed within 0.6  $\mu\text{s}$  which is the time required to scan the coherence gate through a 40  $\mu\text{m}$  distance. The time between two consecutive A-scans is about 16 20 0.6  $\mu\text{s}$ , which is determined by the rotational speed of the mirror 16 of the system and the number of A-scans per image. Thus, the resultant image should be crisp since the motion during 16  $\mu\text{s}$  is 0.08  $\mu\text{m}$  which is much less than the resolution. Accordingly, there should be no motion blurring in the image but a motion artifact may still exist. The resultant motion artifact may 25 be a geometric deformation of the features being imaged that may be as large as 63  $\mu\text{m}$  depending on the size of the feature and the target velocity. This motion artifact is due to the effect that the air-tissue interface has on the optical radiation from the plurality of optical sources 50.

As illustrated in Figure 9, the focal point of an individual fiber of 30 the apparatus, inside the tissue being imaged, can vary depending on the distance  $d_0$  of the location of the focal point in the tissue, whether the tissue surface had a refractive index of 1, and the actual refractive index of the

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tissue (which is typically approximately 1.4). Accordingly, the actual focal point is at a distance  $d_f$  below the tissue surface given by:

$$d_f = d_0 \frac{\tan \theta_i}{\tan \theta_a} = d_0 \frac{\tan \theta_a}{\tan \left[ \sin^{-1} \left( \frac{n_1 \sin \theta_a}{n_2} \right) \right]} \quad (15)$$

where  $\theta_i$  is assumed to be equal to  $\theta_a$ , the acceptance angle of the individual fibers and  $\theta_2$  will be determined by the refractive index  $n_1 = 1$  (i.e. air) outside the tissue and  $n_2 = 1.4$  inside the tissue.

The coherence gate location varies according to:

$$d_c = \frac{n_1}{n_2} d_0 \quad (16)$$

Accordingly, due to the fact that optical radiation travels more slowly in a medium with a larger refractive index there is an optical path mismatch between the focal point and the coherence gate of an optical beam which is matched in a medium with  $n_1 = 1$  (i.e., with no tissue present). This mismatch is:

$$\Delta d = n_2(d_f - d_c) = \frac{n_2 d_0 \tan \theta_a}{\tan \left[ \sin^{-1} \left( \frac{\sin \theta_a}{n_2} \right) \right]} - d_0 \quad (17)$$

15 A tissue refractive index of  $n_2 = 1.4$  yields  $\Delta d = 0.97 d_0$ . This mismatch problem is common for all high-NA OCM systems and many existing high-NA OCM systems use some form of dynamic compensation, i.e., changing the reference path length dynamically to compensate for  $\Delta d$ , however, such dynamic compensation is difficult with a high imaging speed. Accordingly,  
20 one aspect of the embodiment of the present invention is to use 'flexible triggering' of the detected interferogram signal.

As shown above, the free space group path length difference is  $2\Delta l_g = 1.24$  mm peak to peak, which is much larger than the useful A-scan range of only 40  $\mu\text{m}$ . This leaves room for dealing with the mismatch since  
25 one then can trigger to obtain the interferogram only when the coherence gate is passing through the focal point.

As shown in Figure 9, the working distance for each fiber channel,  $d_w$ , varies with  $n_2$ , which is approximately constant. Therefore, if one knows

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where the tissue surface is,  $d_0$  can be determined and in turn  $\Delta d$  can be determined.

Referring to Figure 10, showing a perspective view of a tissue surface and an arbitrary axial line 90, channel 1, which is designated to scan the surface of the tissue, is the first to pass through the axial line 90, in the scan area 28. The focal points of channels 1 and 2 are indicated at 91 and 92 in a schematic representation 94 of the optical radiation from the multiple single mode fibers 10 (i.e. channels) passing through the axial line 90. The focal point of the last channel, i.e. channel 50 in this example, is indicated at 95 and is designated to scan the deepest layer of the tissue in the image. The overall profile of the representation 94 defines a flexible trigger zone, within which the coherence gate and the focal length can be matched. One of the 50 channels, i.e. channel "v", will experience a large and distinctive specular reflection since the air-tissue interface approximates a mirror and reflects incident light. Underneath the tissue surface, the tissue acts as a turbid media which scatters and absorbs incident optical radiation. Thus, channel "v" will determine  $d_0$  for this particular axial line 90 since all of the channels before channel "v" will return a signal that is at noise level. Accordingly, the "flexible triggering" method comprises comparing the detected reflected optical radiation for adjacent channels to locate the tissue surface by identifying the channel in which there is a large increase in reflectance compared to its 'neighboring' channels. This information is then passed on to each of the subsequent channels and the trigger point for each channel is set accordingly to reduce mismatch between the focal point and the coherence gate.

As an example, if channel "v" is channel 13 then the apparatus is calibrated such that channels 1 to 12 are set to scan free space above the tissue surface, channel 13 to scan the tissue surface, and subsequent channels are set to scan deeper tissue, with no mismatch between the focal point and the coherence gate of the optical beam of each channel. During imaging, a tolerance of  $\Delta d_0 = \pm 0.5$  mm of the location of the tissue surface can be allowed as indicated at 96 in Figure 10. This tolerance is related to

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the A-scan performance and the frequency response of the envelope detector as will now be explained.

Given  $\Delta d_b = 0.5$  mm, the mismatch that needs to be compensated for is given by:

$$5 \quad \Delta d'' = 0.693 \times 0.5 = 0.347 \text{ mm} \quad (18)$$

This means that instead of triggering the interferogram signal at the maximum carrier frequency, the actual carrier frequency needs to be:

$$f_c' = f_{cmax} \cos(\sin^{-1}(\Delta d''/\Delta l_0)) = 13.5 \text{ MHz} \quad (19)$$

which is about 83% of the maximum carrier frequency with the 10 interferogram signal bandwidth changing accordingly. Although the envelope detector's frequency response can be tuned dynamically, it is simpler and faster for the envelope detector to have a fixed response but it was designed for a 17% tolerance of the cut-off frequencies. In this way, the 15 entire flexible triggering scheme contains only fixed components and all of the compensation is performed electronically to satisfy the high imaging speed requirement.

The optical components shown in Figure 6 can be chosen as follows. Based on Boppart, S.A., Bouma, B.E., Pitris, C., Southern, J.F., Brezinski, M.E., and Fujimoto, J.G. (*In vivo Cellular Optical Coherence Tomography Imaging*, Nature Medicine, Vol. 4 No.7:861-865, July 1998), an SNR of greater than 100 dB can be achieved in a non-endoscopic OCT system using 2 mW of incident power on the tissue to allow for imaging to a depth of approximately 2 to 3 mm. The optical source used was a Kerr-lens mode-locked solid-state Cr<sup>4+</sup>: forsterite laser operating at a 1280 nm center 25 wavelength with a coherence length of 5.1 μm. However, the embodiment of the present invention is not limited to this type or any other particular type of source, such as a broadband superluminescent diode. For instance, another possibility is a white-light emission Cr:LiSAF optical source with a 30 bandwidth of approximately 100 nm centered at 860 nm which will provide a coherence length of approximately 4.5 to 6 μm. This diode-pumped, solid-state, mode-locked laser should operate with a pulse-repetition rate of about 100 MHz and an average power of 30 mW when operated at 860 nm.

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The pulse energy variation should be less than 1%. Several (e.g., 2 or 4) of these lasers as indicated at 50 in Figure 6 are needed to provide the total power requirement of the 50 channels. The channels scanning the deeper portion of the tissue will need about approximately 1 to 2 mW of incident power per channel and the channels scanning the shallower portion will need less. The tree couplers 52 can be configured to split the source power to match these requirements. Since the maximum carrier frequency is 16.3 MHz, each interference fringe will contain at least 6 laser pulses. Therefore the fringe pattern should be adequately sampled.

For each channel, a separate photo receiver or detector 58 may be used to detect the interference fringes. The maximum detector bandwidth is 125 MHz, although in the apparatus of the present invention, a detector bandwidth of 30.8 MHz may be sufficient, as determined by the carrier frequency and the bandwidth of the interferogram.

An alternate embodiment of the present invention involves the concept of sharing optical components to reduce device complexity and cost. Referring to Figure 11a, a typical single channel interferometer 150 with balanced detection in which the AC component of the interferogram is separated from the DC component of the interferogram and only the AC component is amplified is shown. The single channel interferometer 150 comprises an IR broadband light source L, a visible wavelength guide light G, a balanced detector BD, a polarization controller PC, a phase modulator MOD and an optical delay generator ODG which are connected through a network of optical fibers and 3 dB couplers 140, 142 and 144. The "x" denotes a dead end in the fiber network. The visible wavelength guide light G may be a green laser which indicates the direction in which the single channel interferometer 150 is pointing (i.e. it indicates what will be imaged). The single channel interferometer 150 is connected to a sample S.

The design of Figure 11a can be extended to construct a two channel interferometer 160 as shown in Figure 11b. The subscripts denote the components that are in the two channels. A component without subscripts indicates that the component is used in both channels. The two

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channel interferometer 160 comprises a laser L', a visible wavelength guide laser G', a 2 to 1 tree coupler TC1, polarization controllers PC<sub>1</sub>, PC<sub>2</sub> and phase modulator φMOD', variable delay elements VD<sub>1</sub> and VD<sub>2</sub>, an optical delay generator ODG', detectors BD<sub>1</sub> and BD<sub>2</sub> and 3 dB couplers 162, 164, 166, 168, 170 and 172. The variable delay elements VD<sub>1</sub> and VD<sub>2</sub> are introduced to adjust the coherence gate positions for each channel. The two channels are coupled to samples S<sub>1</sub> and S<sub>2</sub> which may be two points at different locations in a tissue sample. The light source L' is shared between the two channels in this case, with the optical power in channel 1 being twice that in channel 2. Therefore, channel 1 should be used to scan a deeper region of tissue than channel 2. The 1 to 2 tree coupler TC1 is used so that both channels can share the same reference arm (comprising the phase modulator φMOD' and the optical delay generator ODG'). The ability to share the same reference arm allows one phase modulator to be used to phase modulate the optical radiation from the multiple single mode fibers 10 (i.e. all the channels). Note that the two channels are combined into one fiber by the tree coupler TC1 and then fed to the same phase modulator φMOD'. Accordingly, cost and complexity of the two channel interferometer 160 is reduced.

Based on Figure 11b, it is conceivable that a general optical network can be used to construct an N channel OCT system such as optical network 180 shown in Figure 11c. The optical network 180 comprises an optical network for an n<sup>th</sup> channel 182 and a reference arm 184 that is shared by all n channels. The optical network for the n<sup>th</sup> channel 182 comprises a detector BD<sub>n</sub>, 3 dB couplers 194, 196 and 198 and a sample arm comprising a polarization controller PC<sub>n</sub> and a variable delay element VD<sub>n</sub> connected to a sample S<sub>n</sub>. The optical network for the n<sup>th</sup> channel 182 receives optical source radiation 186 from the n-1<sup>th</sup> channel and transmits optical source radiation 188 to the n+1<sup>th</sup> channel via 3 dB coupler 194. The optical network for the n<sup>th</sup> channel 182 receives guide light power 190 from the n-1<sup>th</sup> channel and sends guide light power 192 to the n+1<sup>th</sup> channel via 3 dB coupler 196. In this embodiment, a light source (not shown) may be

shared between each of the N channels with a power distribution that follows a geometric series or another suitable power partition scheme. The reference arm 184, comprising an N to 1 tree coupler TC<sub>n</sub>, a phase modulator φMOD" and an optical delay generator ODG", is shared between 5 each of the N channels.

Each of the schematics shown in Figures 11a, 11b and 11c, suffer from the fact that a portion of the optical radiation of the interference pattern, from the interference between the reflected optical radiation from the sample and reference arms, which is sent from the 3 dB coupler 10 connected to the detector is lost. In this case 50% of the optical radiation of the interference pattern is lost since a 3 dB coupler is used. For instance in Figure 11a, only 50% of the optical radiation of the interference pattern is sent from 3 dB couplers 140 and 142 to the detector BD. This makes it more difficult to detect the interference pattern especially for interference 15 patterns with low intensities. To address this, a non-reciprocal optical device, such as an optical circulator may be used to send, to a detector, the portion of the optical radiation that would have been lost if only a 3 dB coupler were used.

Referring to Figures 12a, 12b and 12c, alternate embodiments of 20 a single channel OCT device 200, a two channel OCT device 210 and an optical network for an N channel OCT device 220 are shown comprising optical circulators. In Figures 12a, 12b and 12c, the optical circulators C, C<sub>1</sub>, C<sub>2</sub> and C<sub>n</sub> are used to salvage and direct the optical radiation of the interference pattern to the detectors BD, BD<sub>1</sub>, BD<sub>2</sub> and BD<sub>n</sub>, respectively to 25 provide a larger intensity interference signal for detection. The rest of the components in these embodiments are similar to those in the of the single channel OCT device 150, the two channel OCT device 160 and the optical network for the N channel OCT device 180 shown in Figures 11a to 11c. The concept of using optical circulators to salvage optical radiation and 30 provide the salvaged optical radiation to a detector may also be applied to the apparatus of Figure 6 in which optical circulators could be placed between the 3 dB couplers and the detectors.

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The schematic shown in Figure 11c and 12c leads to an elegant design, however, parallel interferometers that share components (i.e. a phase modulator) may produce prohibitive amounts of channel cross talk which may consequently lead to image degradation. However, with fiber length mismatching between channels, cross talk may be effectively handled. Electronic cross-talk can be handled using standard shielding and grounding techniques. The following describes the optical cross-talk.

Referring now to Figure 13a, a two channel OCT system 230 was assembled to investigate channel cross talk. The two channel OCT system 10 230 comprises a laser  $L_E$ , detectors  $D_1$  and  $D_2$ , beam splitters  $BS_1$  and  $BS_2$ , a 1 to 2 tree coupler  $TC_E$ , a phase modulator  $PM_E$ , an optical delay generator  $ODGE$ , beam collimators  $BC_1$  and  $BC_2$  and two mirrors  $S_{1E}$  and  $S_{2E}$  which simulate samples. In the two channel OCT system 230, the desired imaging signals come from the channel 1 and channel 2 optical paths. The desired imaging signal for channel 1 occurs when light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_1 \rightarrow D_1 \quad (20)$$

interferes coherently with light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow ODGE \rightarrow BS_1 \rightarrow D_1 \quad (21)$$

and is detected by the detector  $D_1$ . The desired imaging signal for channel 2 occurs when light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow S_2 \rightarrow BS_2 \rightarrow D_2 \quad (22)$$

interferes coherently with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODGE \rightarrow BS_2 \rightarrow D_2 \quad (23)$$

and is detected by the detector  $D_2$ . Furthermore, OCT imaging in the two channels occurs only when the optical distance  $BS_1 \rightarrow S_1$  is equal to the optical distance  $BS_1 \rightarrow ODGE$  and when the optical distance  $BS_2 \rightarrow S_2$  is equal to the optical distance  $BS_2 \rightarrow ODGE$ . Otherwise, image degradation could occur from constructive interference of light reflected from two (or more) different paths that are not the desired imaging paths stated above.

Based on the optical network shown in Figure 13a, there may be two major classes of potential cross talk. The primary source of cross talk may be coherent light that is reflected (from a mirror or the sample) from

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one channel's beam splitter into the other channel's beam splitter and detector. Such cross talk would have intensities equal to the imaging signal intensities and could potentially cause significant image degradation. Reflection from one channel to the other could occur at the optical delay generator  $ODG_E$  or at the samples  $S_1$  or  $S_2$ . Therefore, light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_1 \rightarrow D_1 \quad (20)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (24)$$

Alternatively, light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow S_2 \rightarrow BS_2 \rightarrow D_2 \quad (22)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow ODG_E \rightarrow BS_2 \rightarrow D_2 \quad (25)$$

Sample arms 1 and 2 would not normally be separated as they are in Figure 13a because the sample arms would be aimed at different points (i.e. different depths) on a tissue sample. When the samples are not separate, reflection could occur from channel 1 into channel 2 and vice-versa. In such a case, light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow S_2 \rightarrow BS_1 \rightarrow D_1 \quad (26)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (21)$$

Alternatively, light from the optical pathway:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_2 \rightarrow D_2 \quad (27)$$

may interfere with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow BS_2 \rightarrow D_2 \quad (23)$$

It should be recalled that reflection may also occur at undesirable locations such as beam splitters and connector insertion points. Conceivably, such reflections may contribute to image noise if the light from these pathways produced interference fringes having a significant intensity. However, this kind of noise may be secondary to the channel cross talk previously described because of its lower intensity.

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Analysis of the system revealed that the worst-case scenario for interference of such back-reflections involves one reflection from a connector. For example, light from the following optical path:

$$L_E \rightarrow BS_1 \rightarrow S_1 \rightarrow BS_1 \rightarrow D_1 \quad (20)$$

5 may interfere with light from the optical pathway:

$$L_E \rightarrow BS_2 \rightarrow ODG_E \rightarrow PM_E \rightarrow ODG_E \rightarrow BS_1 \rightarrow D_1 \quad (28)$$

There are four possible outcomes for the interference of light from any two pathways and the outcome depends on path length difference. Firstly, if the path lengths are identical, then the intensity of the interference 10 fringes at the detector will be greater than the true signal intensity based solely on the sample reflectivity. This sort of image noise would not be detectable as noise and would alter the measured sample intensity throughout the image. Fortunately, the probability of the path lengths matching exactly is remote. A second possibility is that the path lengths 15 could match to within the coherence length of the light source. This situation would result in an increase in the width of the interference fringe envelope and consequently degradation in axial resolution. This situation is unlikely, but it may be detected by measuring the full-width-half-maximum of the mirror surface depth profile. A third possibility involves the path lengths 20 differing by a distance greater than the coherence length of the source  $L_E$  and less than the scanning depth of the optical delay generator  $ODG_E$ . This situation may manifest as two separate coherence envelopes within one depth sweep by the optical delay generator  $ODG_E$ . The final and most likely 25 possibility is that the path lengths differ by more than the scanning depth of the optical delay generator  $ODG_E$  and no noise or extraneous interference fringes will be detected by the system.

The primary type of channel cross talk should be unlikely because of fiber optic manufacturing. Optical path lengths  $BS_1 \rightarrow ODG_E$  and  $BS_2 \rightarrow ODG_E$  are essentially predetermined by the lengths of the fiber pigtails 30 coming from beam splitters  $BS_1$  and  $BS_2$ . Optical path lengths  $BS_1 \rightarrow S_1$  and  $BS_2 \rightarrow S_2$  are deliberately matched to the predetermined corresponding reference arm lengths. Typically manufactured fiber lengths differed by several tens of millimeters which is at least one order of magnitude greater

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than the scanning depth of the optical delay generator **ODG<sub>E</sub>**. Therefore, this type of cross talk should not be a problem in a dual channel system.

In the case of insertion point reflections, if the optical distance **PM<sub>E</sub>** → **ODG<sub>E</sub>** matched the path length difference between optical paths 5 **BS<sub>1</sub>** → **S<sub>1</sub>** and **BS<sub>2</sub>** → **ODG<sub>E</sub>**, then interference fringes and image degradation may occur. Again, this sort of secondary noise should be unlikely because the fiber lengths are about 300 mm while the optical delay generator **ODG<sub>E</sub>** scans through only a couple of millimeters. Furthermore, the intensity of such interference fringes would be lost in the system noise. 10 Secondly, the equipment used has a maximum 0.6 dB insertion loss (in other words a maximum of reflection of 0.6 dB) and therefore such a signal is below the detection limits used in the setup of Figure 13a.

To demonstrate that two channels can use the same fiber and optical components, the OCT system 230 was evaluated. The sample arm 15 mirrors **S<sub>1</sub>** and **S<sub>2</sub>** were placed such that the sample arm optical path length and the optical delay generator **ODG<sub>E</sub>** reference arm optical path length matched for each channel and a set of interference fringes were seen at each of the detectors **D<sub>1</sub>** and **D<sub>2</sub>**. The sample arms for samples **S<sub>1</sub>** and **S<sub>2</sub>** were kept separate for alignment purposes and to eliminate the possibility 20 of light from channel 1 reflecting into the fiber containing channel 2 and vice-versa. Although an optical delay generator could be used to produce both phase modulation and group delay (Tearney et al. 1997), with the setup shown in Figure 13a, the optical delay generator **ODG<sub>E</sub>** was used for group delay (i.e. depth scanning) while the phase modulator **PM<sub>E</sub>** in the 25 reference arm was used to produce phase delay.

In the experimental setup of Figure 12a, the light source **L<sub>E</sub>** comprised a 1310 nm, 9 mW light source (model BBS1310) made by AFC Technologies Inc. The central wavelength of the light source **L<sub>E</sub>** was 1310 nm with a measured spectral spread of ± 40 nm. The measured coherence 30 length of the light source **L<sub>E</sub>** was 10 μm. The detectors **D<sub>1</sub>** and **D<sub>2</sub>** were 155 Mbps Perkin Elmer InGaAs photodiode receivers with a detection band centered at 1310 nm having a bandwidth greater than or equal to 100 nm.

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The phase modulator  $PM_E$  was a JDS Uniphase 43 MHz phase modulator. The beam splitters  $BS_1$  and  $BS_2$  were made by MetroTek. OZ Optics manufactured the beam collimators  $BC_1$  and  $BC_2$ . Alternate suitable components may be used from these or other suppliers.

5 The optical delay generator  $ODG_E$  dispersed the collimated light using a 150 line/mm diffraction grating blazed for 1310 nm which was made by CVI Spectral Products. A Melles Griot glass doublet lens with a 30 mm diameter and 100 mm focal length was used to focus light onto the oscillating mirror. EOPC (Electro-Optical Products Corporation) 10 manufactured the resonant scanner that operated at 8 kHz and scanned through a  $\pm 1^\circ$  mechanical or a  $\pm 2^\circ$  optical angle. This angular setting corresponded to a depth scan of about 1 mm in the sample arms for the samples  $S_1$  and  $S_2$ . Scanning depth is an important consideration in terms of mismatching the optical lengths of the two channels. For instance, if the 15 optical path lengths differ by more than 1 mm then cross talk between the two channels should be minimal and proper shielding and grounding techniques should address electronic cross-talk as well.

Figures 13b and 13c show results from experiments conducted 20 on the setup shown in Figure 13a. Figure 13b shows the oscilloscope trace from the detectors  $D_1$  and  $D_2$  in channel 1 and channel 2. Figure 13b shows that the interference fringes occur at different points in the cycle of the optical delay generator  $ODG_E$  which reflects the slightly different positioning of the two channels within the cycle of the optical delay generator  $ODG_E$ , i.e. the sample arm mirrors  $S_1$  and  $S_2$  were deliberately offset by a small 25 amount to simulate imaging at different depths. Figure 13b shows that there is a strong imaging signal in each of the channels and no evidence of any cross talk. The arrows 232 and 234 indicate reflection from two different sample points which could correspond to two different points in a tissue sample. Furthermore, the full-width-half-maximum of the envelope of each 30 detected pulse corresponded to the coherence length of the light source  $L_E$  which indicates that the light signal in each channel originated from the light source  $L_E$ . Figure 13b shows the experimental results when one of the

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sample points was moved relative to the other sample point. In this case, cross-talk was also not observed.

In another embodiment of the invention, the fiber optic network, previously disclosed herein, is incorporated into an endoscope so that the 5 multi-channel OCT methodology may be used clinically. Due to the size of the fiber bundle tip 12 of the apparatus, the fiber bundle tip 12 will not fit into the working channel of a conventional diagnostic endoscope (although it may be incorporated into the larger-diameter therapeutic endoscopes). Therefore, an alternate design approach was taken. Instead of designing 10 the fiber bundle tip 12 to accommodate the working channel of a conventional diagnostic endoscope, all of the functionality of a conventional diagnostic endoscope was designed around the fiber bundle tip 12. As shown in Figure 14, one embodiment of a GI endoscope 300 (corresponding to the tip 56 of Figure 6) incorporating the endomicroscope 15 of the present invention is approximately 11 mm in diameter. This is slightly larger than the conventional diagnostic endoscope which is 8 - 9 mm in diameter. The GI endoscope 300 has the endomicroscopy capability disclosed above in addition to conventional forward-viewing white light imaging. Therefore, a user of the GI endoscope 300 should be able to 20 obtain a 2 by 2 mm cross-sectional image as illustrated in Figure 16.

The GI endoscope 300 includes a 2.7 mm diameter suction/biopsy channel 302. The end of the suction/biopsy channel 302 is bent so as to present an opening 304 directed towards the tissue area of interest 306. The axis of the suction/biopsy channel 302 may be on the 25 order of 6.7 mm from the center of the tissue area of interest 306. Two channels 308 and 310 are provided for white light illumination and a channel 312 is provided for white light endoscope forward viewing. Each of the channels 308, 310 and 312 may have a diameter of 2.7 mm. A small channel 314 is also provided for an air or water nozzle.

In accordance with the present invention, a side-viewing Endoscopic Coherent Optical Microscope (ECOM) 316 is provided in the GI 30 endoscope 300. The side-viewing ECOM 316 includes a drive mechanism 318 for rotating the mirror 18 (not shown in Figures 14 and 15). As

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mentioned previously, radial, translational or helical scanning may be employed. Furthermore, as previously mentioned, a MEMS drive mechanism may be used instead of a mechanical drive mechanism. The side-viewing ECOM 316 is configured to scan through the tissue area of interest 306 having the depth set by the boundaries 320 and the angular extent set by the boundaries 322. Additionally an optical window 324 may be provided for the side-viewing ECOM 316 (see Figure 14).

The forward-viewing white light channel 312 is updated at a rate of 30 frames/sec. The cross-sectional images obtained by the side-viewing ECOM 316 are updated at 4.4 frames/sec. All imaging channels are displayed simultaneously. The images that may be generated by the GI endoscope 300 are illustrated in Figures 16 and 17. Figure 16 shows a simulated image of a human colon epithelium incorporating the expected spatial resolution which may achievable with the side-viewing ECOM 316. Figures 17a and 17b are a comparison of microscopy imaging versus *in vivo* OCT imaging. Figure 17a has two panels which each show a microscopy image of sweat ducts in the human skin. Figure 17b has three panels which each show an *in vivo* OCT image of sweat ducts in the human skin. The *in vivo* OCT images were generated with a light source operating at a wavelength of 1300 nm.

Typical maneuvers or use of the GI endoscope 300 by an endoscopist will incorporate the following steps:

- a) Following the steps of a general endoscopy procedure, the GI endoscope 300 is inserted under the guidance of the conventional forward-viewing white light channel 312. This maneuver should be no different from that of currently available GI endoscopes.
- b) When the endoscopist needs to make microscopic examinations, he/she first pushes the GI endoscope 300 into contact with the wall of the lumen as shown in Figure 13. The optics are designed such that when the GI endoscope 300 is in contact with the tissue, the correct working distance of the entire optical system is obtained. Although the GI endoscope 300 is in contact with the

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wall, the part of the tissue under microscopic examination is not as illustrated in Figure 15. Therefore, the surface features of the tissue are not distorted by contact pressure. However, this does not imply that the GI endoscope 300 can only be operated in a contact mode. In fact, the GI endoscope 300 may be operated in a non-contact mode, as long as images are formed, which is dictated by whether the previously described dynamic triggering algorithm has found an air-tissue interface. If the air-tissue interface lies within the working distance of the system then the interface should be specific and easily detected since the interface produces clear peaks in the detected light pattern as previously described in the 'flexible triggering' method.

10 c) If the endoscopist needs to examine a region adjacent to the area imaged in step (b), then the endoscopist can torque the GI endoscope 300 and rotate the field of view to a new location.

15 The best techniques currently in use for visualization of the gastrointestinal (GI) tract include endoscopic ultrasonography (EUS) and magnification endoscopy (ME). The resolution of high-frequency EUS, approximately 70 to 100 mm, is insufficient for the identification of many conditions that perturb tissue microstructure, most notably subtle pathologic changes arising within the superficial layers of the GI tract (mucosa and submucosa). ME, with a magnification of up to 170X, provides excellent images of fine superficial mucosal patterns but subsurface structures and lesion staging cannot be determined. Accordingly, tissue biopsy and histology currently remain the standard of care for detecting microscopic diseases involving the GI tract.

20 25 30 The side-viewing ECOM 316 disclosed herein may achieve real-time, 2 mm deep cross-sectional images of the GI wall at a resolution of 5  $\mu\text{m}$  in both axial and transverse (lateral) dimensions. For reference, gastrointestinal epithelial cells average 7 to 10  $\mu\text{m}$  in size which increases further as dysplastic or neoplastic transformation ensues. In the GI tract, a depth of view at 2 mm is nevertheless sufficient to detect mucosally-based

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diseases as well as any neoplastic invasion into the underlying submucosa, which is of important for prognostic and therapeutic purposes. The image resolution of the side-viewing ECOM 316 may correspond to observing an *unstained histology slide under a 100X (total magnification) microscope.*

5 Accordingly, many important entities such as dysplasia (cellular neoplastic alterations) or neoplastic violation of structures such as the lamina propria or muscularis mucosae may be discernible with the side-viewing ECOM 316.

The present invention may allow for *in-situ* diagnosis of diverse 10 *microscopic* mucosal pathologies and lesion staging. In essence, this "optical biopsy" technique may replace, or at the very least, guide the standard biopsy and histology method. This may translate into reducing unnecessary biopsy samples and tissue processing, decreasing patient risk and increasing sampling rate and diagnostic yield thus providing immediate 15 diagnostic feedback both to the physician and the patient and targeting biopsies (which in itself may become a therapeutic maneuver in some cases). Pre-neoplastic GI conditions such as Barrett's esophagus, chronic ulcerative colitis, early flat adenomas, or foci of aberrant colonic crypts, to name a few, may be applicable to the side-viewing ECOM 316. Currently, 20 detection and surveillance of neoplastic progression within these conditions are suboptimal due to their microscopic nature.

Secondly, the side-viewing ECOM 316 may serve as a functional 25 imaging system permitting monitoring of neoplastic and non-neoplastic tissue alterations over time. For instance, the recovery of the structure of small intestinal villi and reduction in inflammatory cells may be monitored by the side-viewing ECOM 316 in diverse malabsorptive disorders of the gut such as gluten-sensitive enteropathy, tropical sprue and intestinal infestation. The natural history of many mucosal diseases at the microscopic level may also be assessed in a minimally invasive manner. 30 The ability to monitor structural cellular changes that are occurring *in vivo* with time may provide important physiologic information on cellular function and insight into cellular pathologic transformation.

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Thirdly, the side-viewing ECOM 316 may be used in the monitoring of tissue post therapy. *In vivo* microscopic evaluation of surgical resection margins or treatment margins during post-therapeutic surveillance of cancer resection or assessment of the adequacy of photodynamic therapy of mucosal preneoplastic conditions are only some examples.

Applications in other medical specialties may also be possible. It should be understood by those skilled in this art that the multichannel OCT apparatus disclosed herein may have application in a large number of medical specialties such as dermatology, hematology, oncology (medical and radiation), ophthalmology, urology, surgery, respirology and gastroenterology.

The multichannel OCT system disclosed herein may be altered to further improve system performance. For instance a modification that may be made would be to employ coded transmission for the optical radiation which is radiated from the optical sources. This technique may increase the image resolution by increasing the SNR of the optical radiation of the interference pattern obtained in channels which suffer from poor SNR.

It should be understood that various modifications can be made to the preferred embodiments described and illustrated herein, without departing from the present invention, the scope of which is defined in the appended claims. For instance, in each of the schematics, herein disclosed, other optical couplers may also be used in place of the 3 dB couplers.

**CLAIMS:**

1. An apparatus for optical examination of a sample, the apparatus comprising:
  - 5 an optical source means for providing a plurality of separate optical radiation sources;
  - a first optical path extending from the source means;
  - 10 a focusing means in the first optical path for focusing optical radiation from the optical radiation sources into a plurality of respective focal points located on a surface within the first optical path to provide substantially continuous coverage of a selected portion of the first optical path, whereby, in use, a sample can be located at least partially within said selected portion, thereby permitting simultaneous scanning of a plurality of points within the sample.
2. An apparatus as claimed in claim 1, wherein the optical source means comprises a primary optical source and optical coupling means connecting the primary optical source to the optical radiation sources and comprising a plurality of optical fibers.
3. An apparatus as claimed in claim 2, wherein the plurality of optical fibers terminate in a fiber bundle tip, wherein ends of the optical fibers in the fiber bundle tip are stepped relative to one another along the first optical path and wherein optical radiation from each optical fiber is focused to a different focal point.
4. An apparatus as claimed in claim 1, 2 or 3, which includes a rotatable mirror in the first optical path, for deflecting radiation from the optical radiation sources to permit rotational movement of the surface.
5. An apparatus as claimed in claim 1, 2 or 3, which includes a mirror in the first optical path and wherein the optical source means, the

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focusing means and the mirror, in combination, may be linearly translated to permit linear movement of the surface.

6. An apparatus as claimed in claim 1, 2 or 3, which includes a 5 rotatable mirror in the first optical path and wherein the optical source means, the focusing means and the rotatable mirror, in combination, may be linearly translated to permit helical movement of the surface.

7. An apparatus as claimed in claim 4, 5 or 6, wherein the surface is 10 a complex surface.

8. An apparatus as claimed in claims 4, 5 or 6, wherein the mirror is a surface of a prism.

15 9. An apparatus as claimed in claims 4 or 6, including a micromachined electro-mechanical system coupled to the mirror for rotating the mirror.

10. An apparatus as claimed in claim 5 or 6, including a 20 micromachined electro-mechanical system for linearly translating the optical source means, the focusing means and the mirror.

11. An apparatus as claimed in claim 2, 3 or 4, which further includes 25 a plurality of optical couplers between the primary optical source and the optical fibers, an optical delay generator coupled to the optical couplers and detector means coupled to the optical couplers, wherein the optical couplers transmit a portion of the radiation from the primary optical source along the first optical path and a portion of the radiation from the primary optical source to the optical delay generator, the optical delay generator providing a 30 second optical path, wherein an interference effect occurs between radiation returned along the first and second optical paths to the optical couplers and the optical couplers transmit the radiation returned along the first and second optical paths to the detector means.

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12. An apparatus as claimed in claim 11, which includes a plurality of primary optical sources and a plurality of tree couplers, each tree coupler being associated with one primary optical source and coupling said one primary optical source to at least one of the optical couplers.
13. An apparatus as claimed in claim 12, which includes a plurality of optical circulators, placed between the optical couplers and the detectors for providing salvaged optical radiation to the detectors.
14. An apparatus as claimed in claim 11, wherein a plurality of optical fibers couple the optical couplers to the optical delay generator, the optical delay generator having a grating and a scanning mirror, the scanning mirror having an axis, wherein the grating separates optical radiation from each optical fiber into spectral components linearly oriented on the scanning mirror, wherein the midpoint of said spectral components is offset from the axis of the scanning mirror by a distance  $x_d$  to phase modulate said spectral components.
15. An apparatus as claimed in claim 11, which includes a first plurality of optical fibers for coupling each optical coupler to a phase modulator and a second plurality of optical fibers for coupling each phase modulator to the optical delay generator, the optical delay generator having a grating and a scanning mirror, the scanning mirror having an axis, wherein for each optical fiber, the phase modulator phase modulates the optical radiation and said grating separates said phase modulated optical radiation into spectral components which are linearly oriented on said scanning mirror, the midpoint of said spectral components being centered on the axis of said scanning mirror and wherein the spectral components from each optical fiber is spaced apart from the spectral components of the optical radiation from the other optical fibers.

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22. An N channel apparatus as claimed in claim 21, wherein the sample arm comprises a polarization control means, a variable delay element and a sample.
- 5 23. An N channel apparatus as claimed in claim 20, wherein the reference arm comprises a tree coupling means, a phase modulating means and an optical delay means.
- 10 24. A two channel apparatus, for optical examination of a sample, said two channel apparatus comprising two optical networks as claimed in claim 20, 21, 22, 23, an optical source and a visible light source for guiding the orientation of the two channel apparatus.
- 15 25. A method for optical examination of a sample, the method comprising:
- (a) providing radiation from a plurality of separate optical radiation sources, along a first optical path;
- (b) providing focusing means in the first optical path;
- (c) focusing the optical radiation from the optical sources into
- 20 a plurality of respective focal points along a surface within the first optical path to provide substantially continuous coverage of a selected portion of the first optical path; and
- (d) providing a sample located at least partially within the first optical path; and
- 25 (e) simultaneously scanning a plurality of points within the sample.
26. A method as claimed in claim 25, which includes providing radiation from a primary optical source and transmitting the radiation along a plurality of optical fibers to a plurality of separate optical radiation sources.
- 30 27. A method as claimed in claim 26, which includes terminating the plurality of optical fibers in a fiber bundle tip, providing the ends of the

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optical fibers in the fiber bundle tip in a common plane and stepping the ends of the optical fibers relative to one another, along the first optical path, and focusing radiation from the optical fibers through a common lens.

- 5        28.      A method as claimed in claim 27, which includes:  
                 (a) providing a rotatable mirror in the first optical path;  
                 (b) deflecting the first optical path;  
                 (c) causing the plurality of focal points to be located on a surface;  
                 (d) performing an axial scan;  
10       (e) rotating the mirror to move the surface; and,  
                 (f) repeating step (d) at least two times and performing step (e)  
between each repetition.
- 15        29.      A method as claimed in claim 27, which includes:  
                 (a) providing a mirror in the first optical path;  
                 (b) deflecting the first optical path;  
                 (c) causing the plurality of focal points to be located on a surface;  
                 (d) performing an axial scan;  
                 (e) linearly translating, in combination, the focusing means, the  
20       plurality of optical radiation sources and the mirror to move the surface; and,  
                 (f) repeating step (d) at least two times and performing step (e)  
between each repetition.
- 25        30.      A method as claimed in claim 27, which includes:  
                 (a) providing a mirror in the first optical path;  
                 (b) deflecting the first optical path;  
                 (c) causing the plurality of focal points to be located on a surface;  
                 (d) performing an axial scan;  
                 (e) simultaneously rotating the mirror and linearly translating, in  
30       combination, the focusing means, the plurality of optical radiation sources  
and the mirror to move the surface; and,  
                 (f) repeating step (d) at least two times and performing step (e)  
between each repetition.

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31. A method as claimed in claims 28, 29 or 30, which includes providing a surface of a prism as the mirror.
- 5 32. A method as claimed in claims 28, 29 or 30, which includes supplying radiation from the primary optical source through a plurality of couplers to the optical fibers, providing an optical delay generator connected to the optical couplers and providing a second optical path, permitting radiation to be transmitted back along the first and second optical paths to the couplers, for forming interference, and transmitting radiation received from the first and second optical paths at the optical couplers to detection means for detection of the interference pattern.
- 10 33. A method as claimed in claim 32, which includes providing a plurality of primary optical sources and, for each primary optical source, a respective tree coupler, and coupling each primary optical source through said respective tree coupler to each of the optical couplers.
- 15 34. A method as claimed in claim 32, which includes providing optical circulator means between the optical couplers and the detection means for providing salvaged optical radiation to the detection means.
- 20 35. A method as claimed in claim 33, which includes providing the apparatus as an endoscope adapted for examining an internal cavity of the body, including at least one of: at least one channel for white light illumination, a white light endoscope forward viewing channel, a suction/biopsy channel and a channel for one of an air nozzle and a water nozzle.
- 25 36. A method as claimed in claims 30, 31 or 32, wherein there is a change in refractive index between a medium containing the optical radiation sources and the sample and for each focal point, a distance mismatch due to the change in refractive index between the coherence gate

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- of each optical radiation source and the focal point in the sample due is obtained according to the steps of:
- (a) scanning optical radiation from the plurality of optical radiation sources in said first optical path such that the focal points of the optical radiation sources are aligned along a path extending from the medium containing the optical radiation sources into the sample;
- 5 (b) detecting the reflected optical radiation for each focal point and,
- (c) locating the focal point for which there is a large change in reflected optical radiation compared to neighboring focal points, whereby, the focal point located in step (c) indicates the location of the interface between the sample and the medium containing the optical radiation sources.
- 10
- 15 37. A method as claimed in claim 36, wherein the method further comprises repeating steps (a) to (c) for each axial scan to obtain proper spatial resolution for the selected scan zone.

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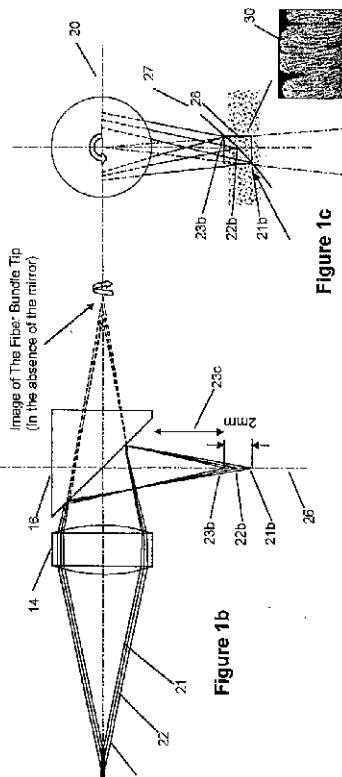
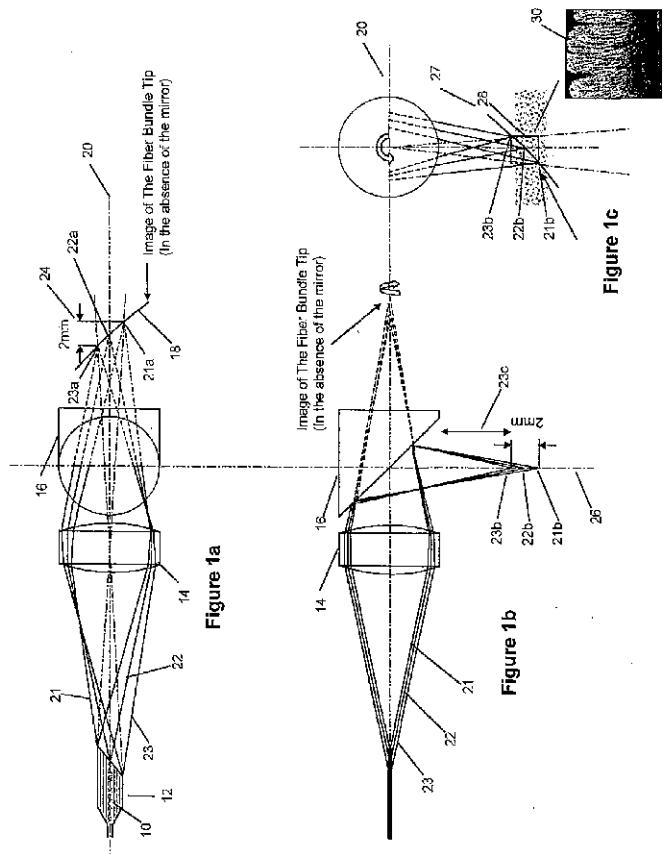


Figure 1c



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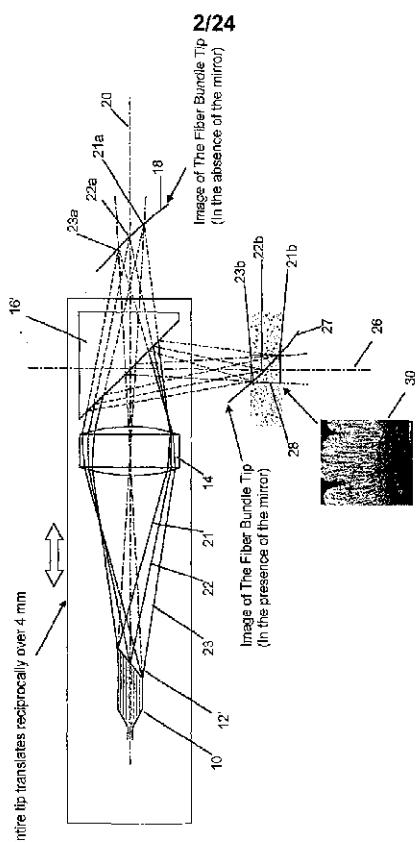


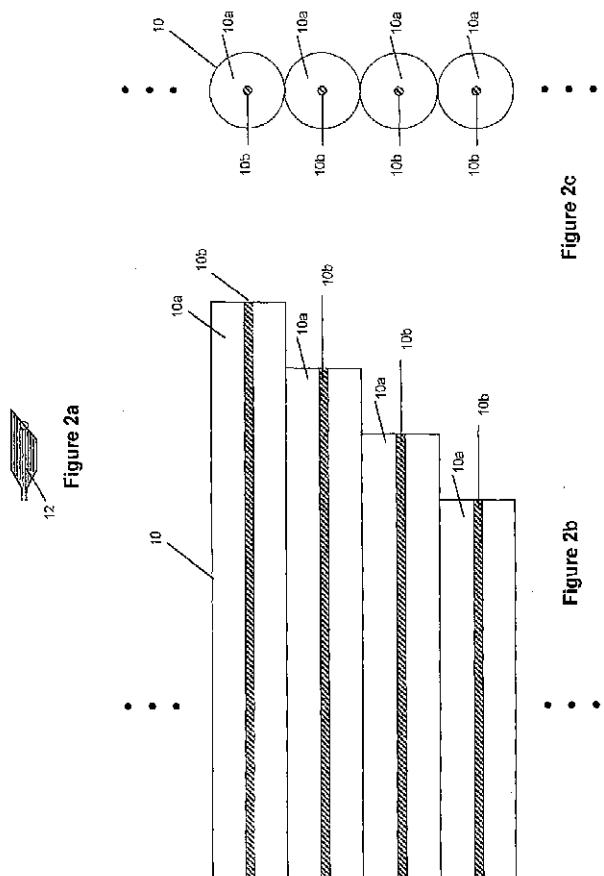
Figure 1d

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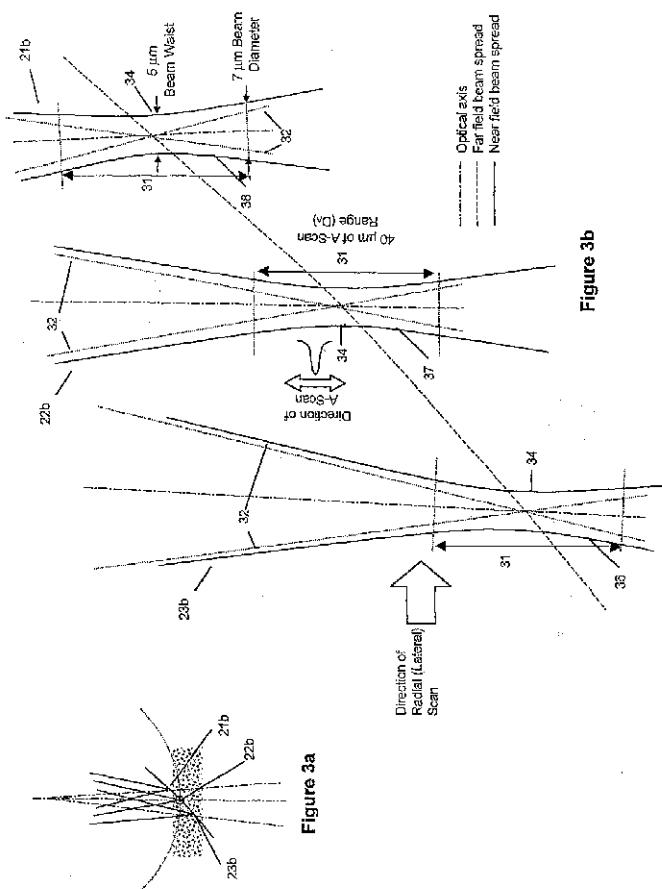
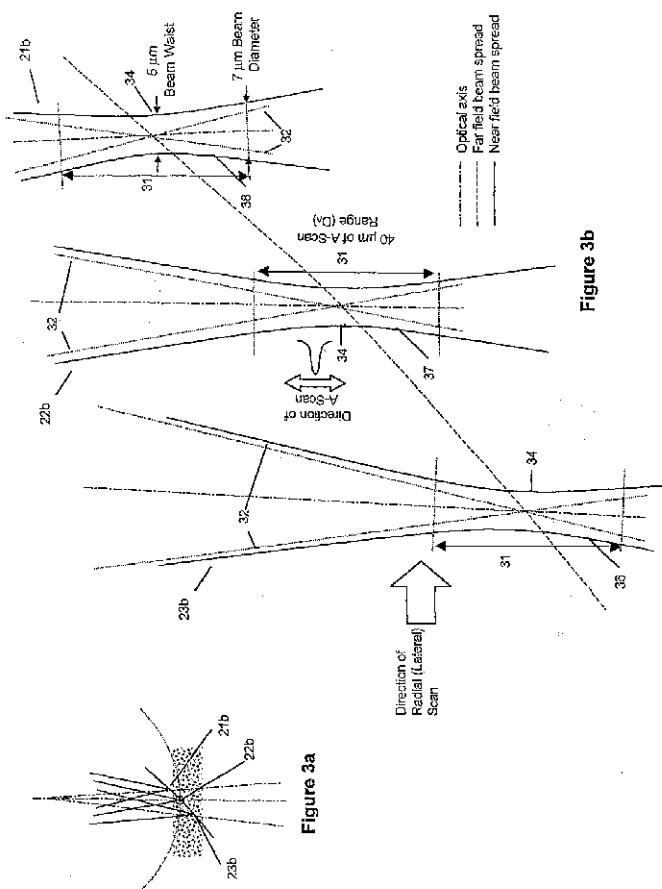


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**Figure 3b**

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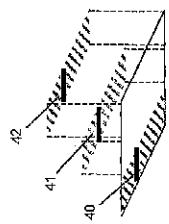


Figure 4f

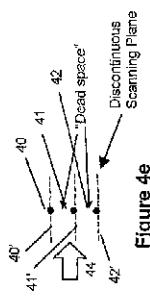


Figure 4e

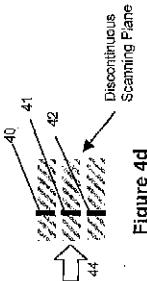


Figure 4d

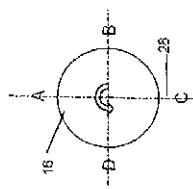


Figure 4a

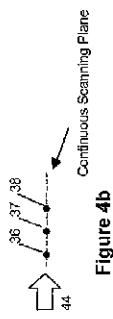


Figure 4b

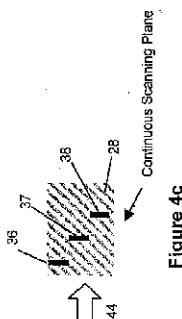


Figure 4c

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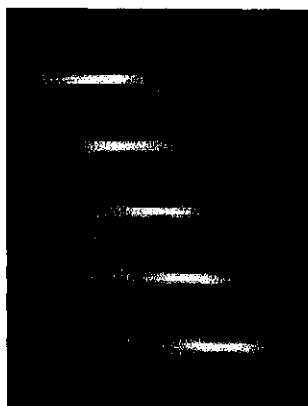


Figure 5b

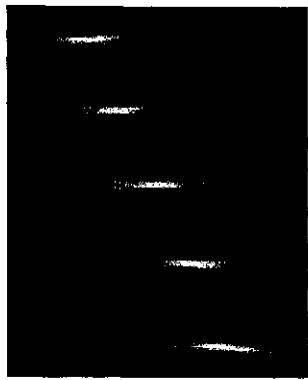


Figure 5a

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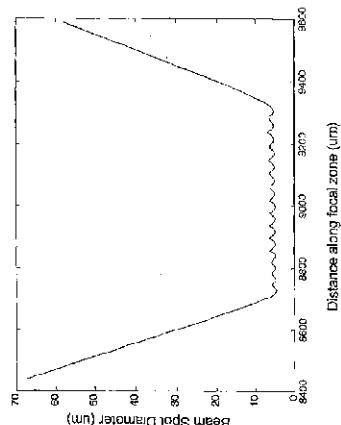


Figure 5d

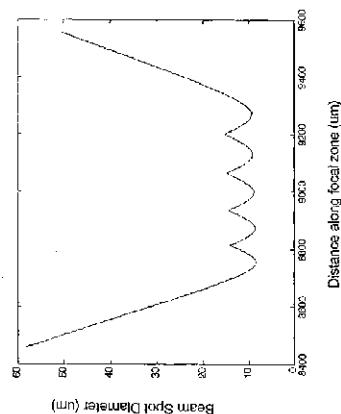


Figure 5c

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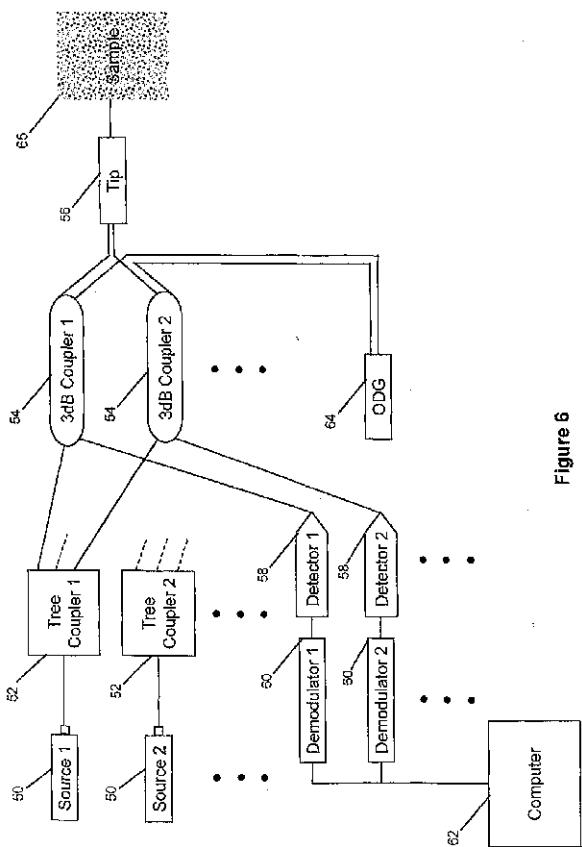


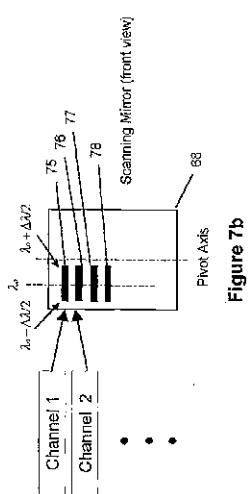
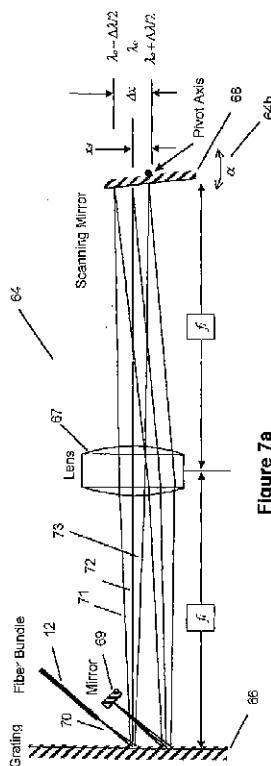
Figure 6

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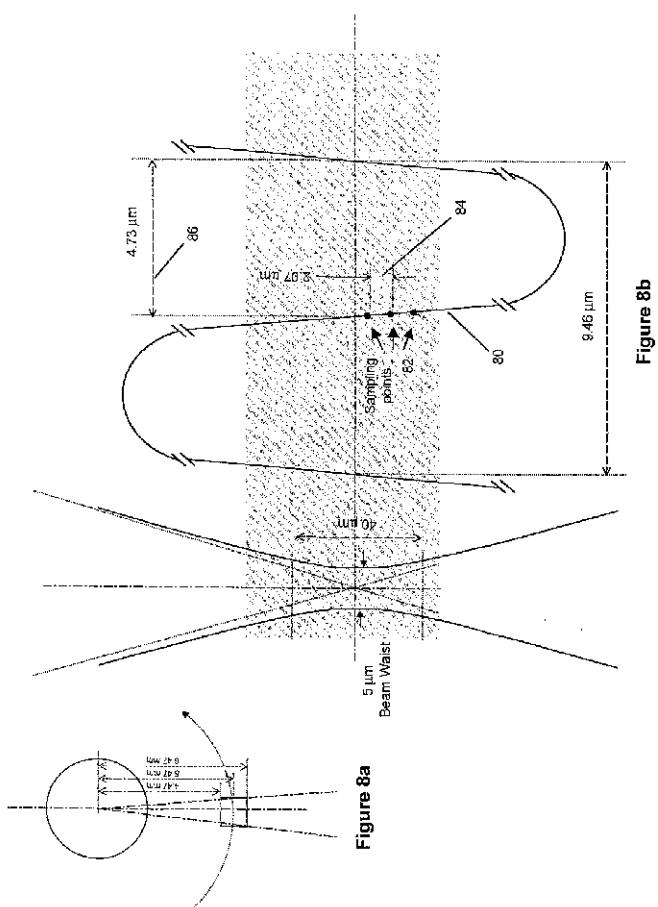


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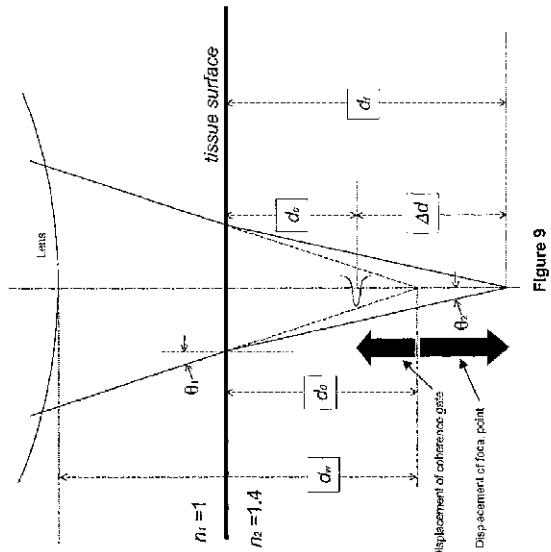


Figure 9

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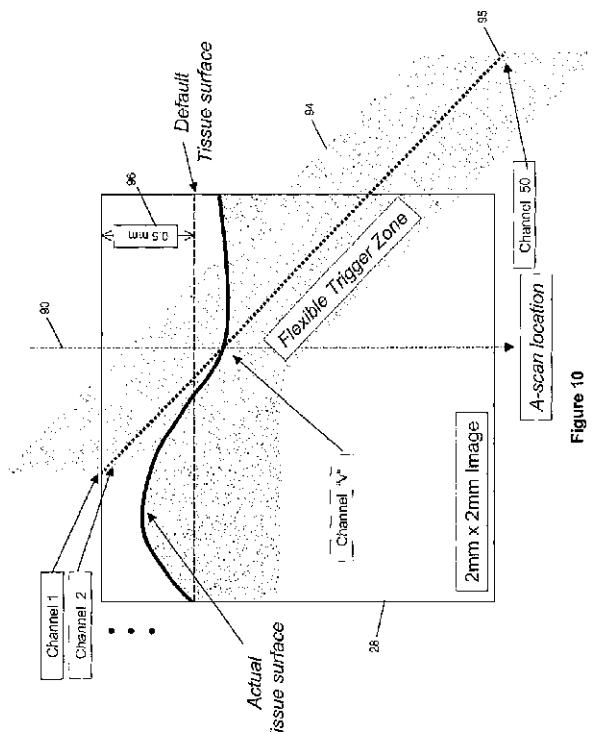


Figure 10

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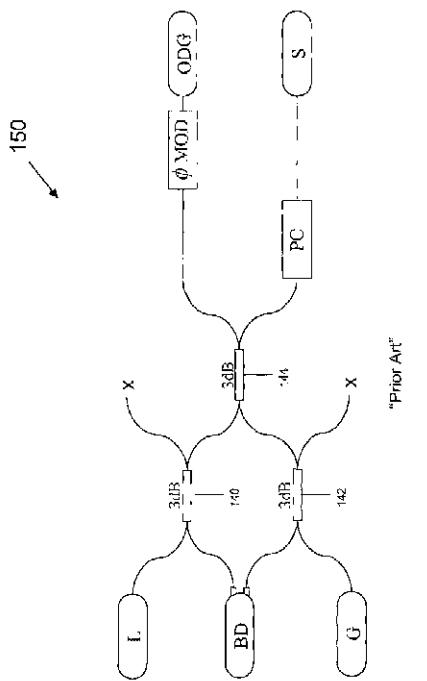


Figure 11a

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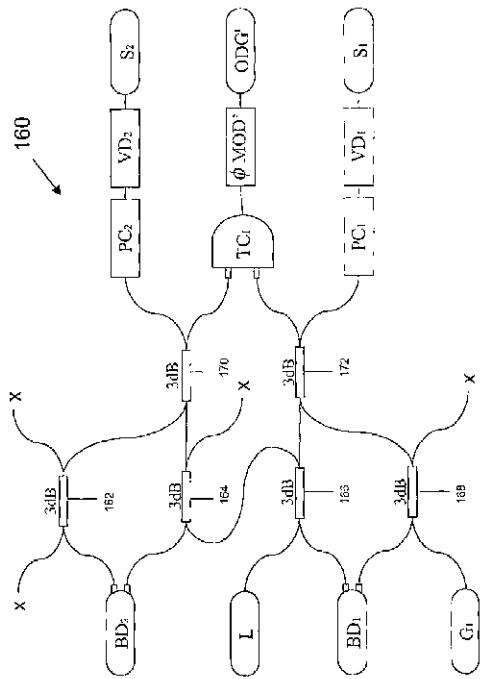


Figure 11b

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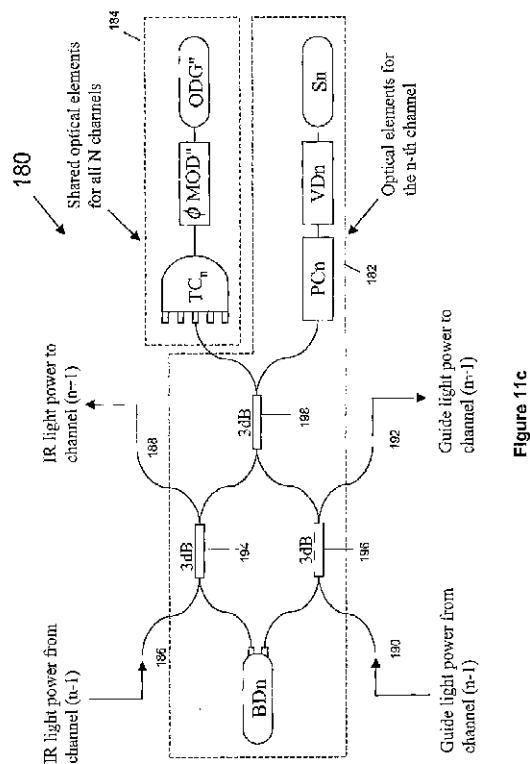


Figure 11c

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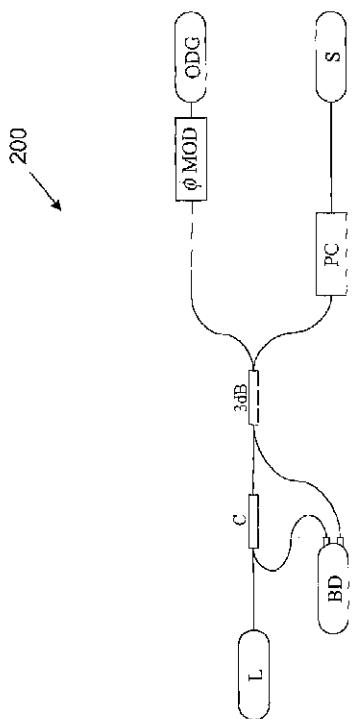


Figure 12a

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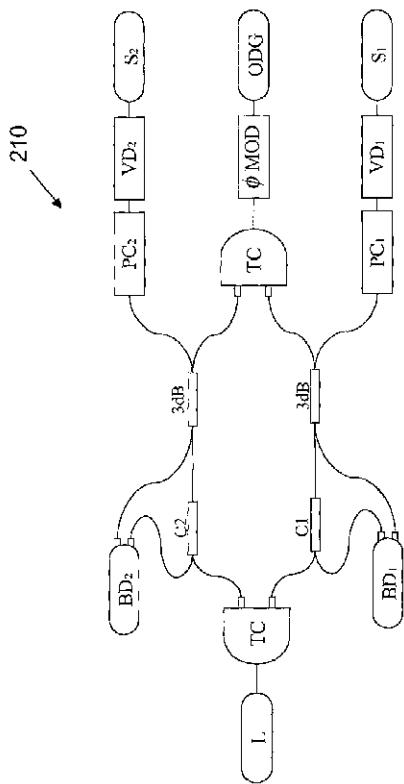


Figure 12b

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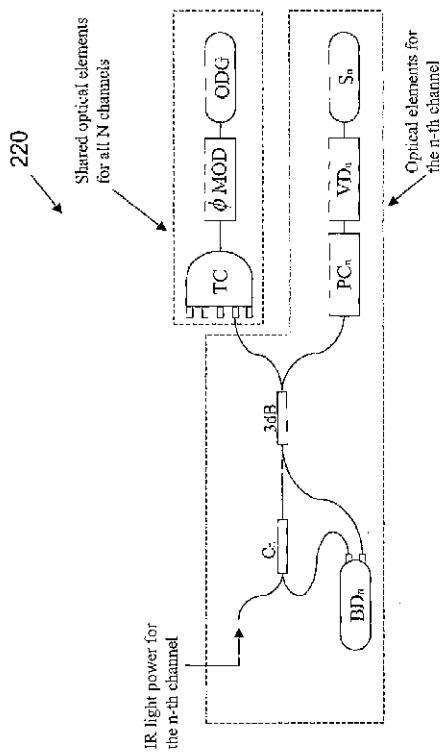


Figure 12c

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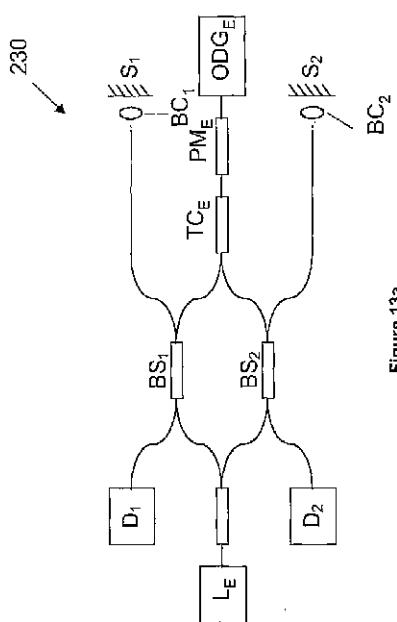


Figure 13a

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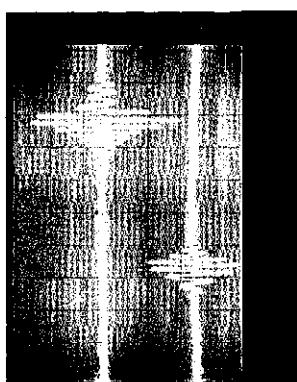


Figure 13c

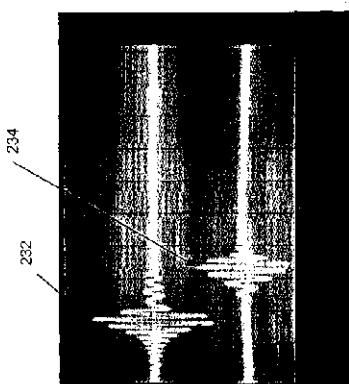


Figure 13b

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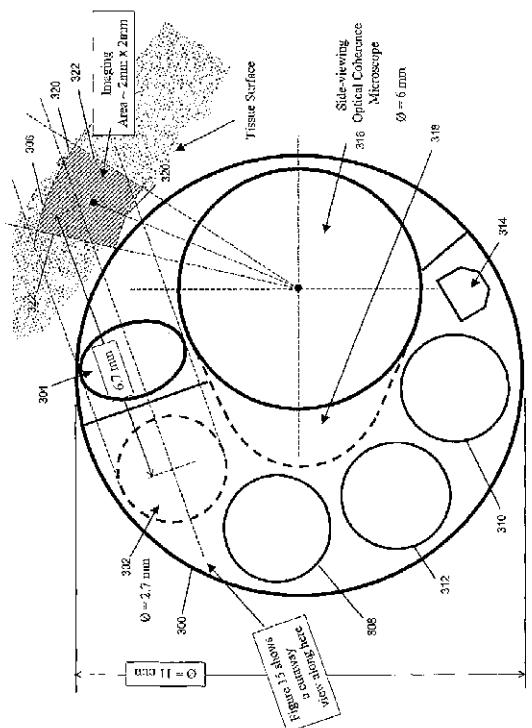


Figure 14

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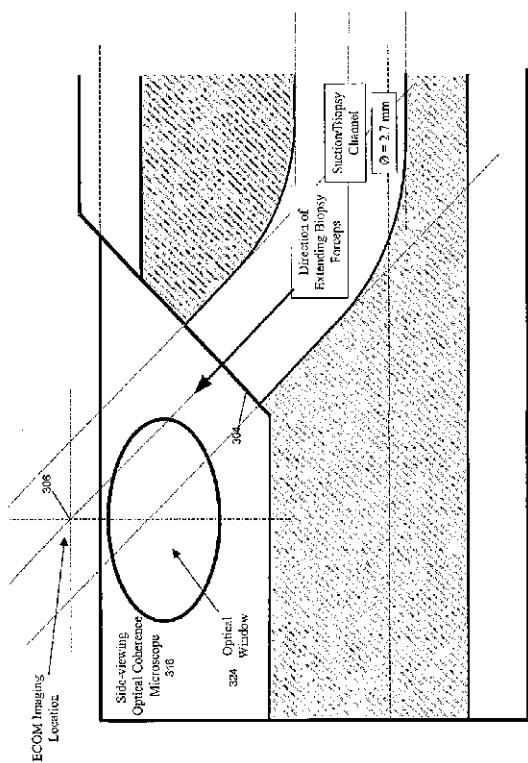


Figure 15

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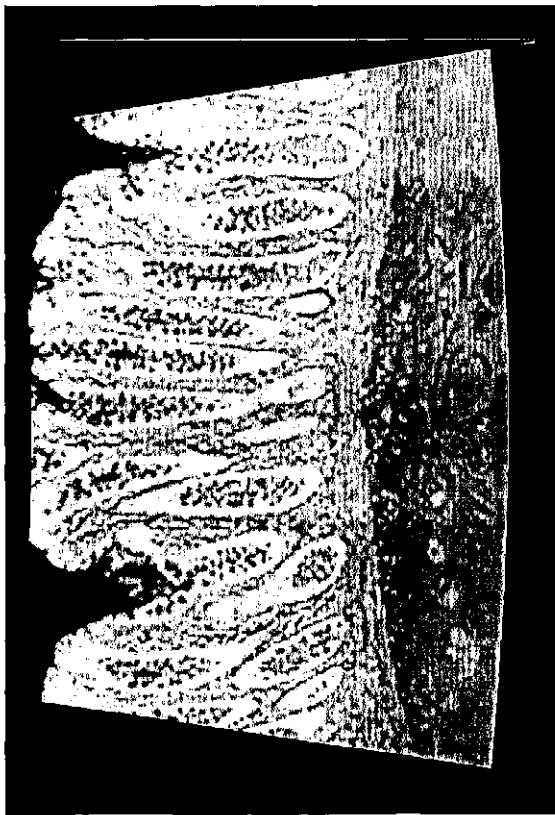


Figure 16

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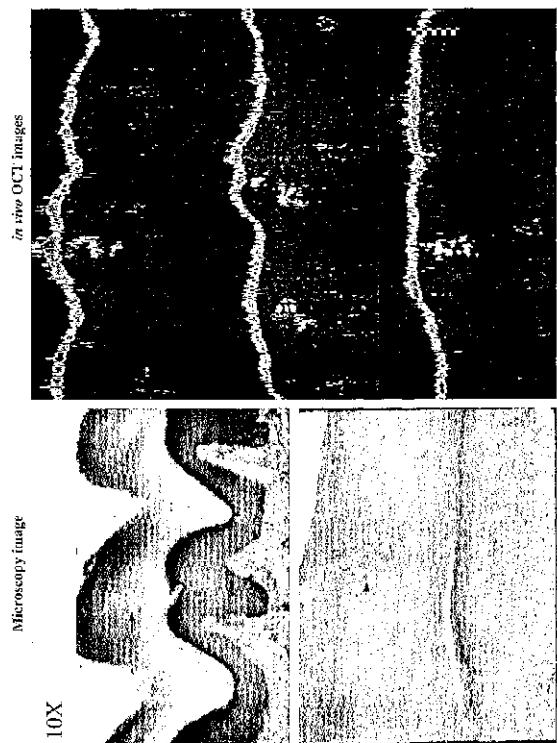


Figure 17b

Figure 17a

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## 【国際調査報告】

INTERNATIONAL SEARCH REPORT		International application No.
<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols)		
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)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Further documents are listed in the continuation of Box C.		
<input type="checkbox"/> See patent family annex. <small>* Special categories of cited documents:</small> "A" document defining the general state of the art which is not considered to be of particular relevance "B" earlier document but published on or after the international filing date "C" document which may show doubts on priority claimed or which is cited to establish the publication date of another citation or other specific reason (as specified) "D" 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		
Date of the actual completion of the international search	Date of mailing of the international search report	
Name and mailing address of the ISA	Authorized officer	
Fax/tele No.	Telephone No.	

Form PCT/ISA/210 (second sheet) (July 1992)

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フロントページの続き

(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

(72)発明者 ヤン , ヴィクター シャオ ドン

カナダ国 エム5エス 3エル1 オンタリオ州 トロント ハーボード ストリート 60 ユニット 936ビー

(72)発明者 ヴィトキン , アイ アレックス

カナダ国 エム6ピー 1イー5 オンタリオ州 トロント グレンレイク アヴェニュー 130

(72)発明者 ウォンキーソン , ルイエ

アメリカ合衆国 ミネソタ州 55901 ロチェスター セカンド ストリート エヌダブリュ211 アパートメント 502

(72)発明者 カツ , シャロン

カナダ国 エム4エム 2エックス2 オンタリオ州 トロント ウィニフレッド アヴェニュー77

(72)発明者 ゴードン , マーガレット レスリー

カナダ国 エム4ピー 2エヌ4 オンタリオ州 トロント デイルウッド ロード 61

(72)発明者 ウィルソン , ブライアン シー

カナダ国 エム6アール 2ワイ6 オンタリオ州 トロント インディアン グローヴ 85

(72)発明者 モク , アルヴィン ホー クアン

カナダ国 エル4ピー 3シー5 オンタリオ州 リッチモンド ヒル スパディナ ロード 187

F ターム(参考) 2G059 BB12 EE09 FF01 FF03 GG01 GG03 GG06 HH01 HH02 HH06

JJ05 JJ11 JJ12 JJ13 JJ15 JJ17 JJ22 KK03 MM01 MM08

MM09

2H040 BA01 CA02 CA11

4C061 CC06 DD03 FF46 FF47 HH51 LL01 WW10 WW20

5C024 BX02 CX00 CY00 EX41 EX48 EX54 JX02

专利名称(译)	<无法获取翻译>		
公开(公告)号	<a href="#">JP2004502957A5</a>	公开(公告)日	2008-07-31
申请号	JP2002509751	申请日	2001-07-10
[标]申请(专利权)人(译)	大学健康网络		
申请(专利权)人(译)	盐湖城大学健康网络		
[标]发明人	ヤンヴィクターシャオドン ヴィトキンアイアレックス ウォンキーソンルイエ カツシャロン ゴードンマーガレットレスリー ウィルソンブライアンシー モクアルヴィンホークアン		
发明人	ヤン,ヴィクターシャオ ドン ヴィトキン,アイ アレックス ウォンキーソン,ルイエ カツ,シャロン ゴードン,マーガレット レスリー ウィルソン,ブライアン シー モク,アルヴィン ホー クアン		
IPC分类号	G01N21/17 A61B1/00 G02B23/26 H04N5/335		
CPC分类号	A61B5/6852 A61B1/00096 A61B1/00172 A61B1/05 A61B5/0066 G01N21/4795		
FI分类号	G01N21/17.620 A61B1/00.300.D G02B23/26.B H04N5/335.V		
F-TERM分类号	2G059/BB12 2G059/EE09 2G059/FF01 2G059/FF03 2G059/GG01 2G059/GG03 2G059/GG06 2G059 /HH01 2G059/HH02 2G059/HH06 2G059/JJ05 2G059/JJ11 2G059/JJ12 2G059/JJ13 2G059/JJ15 2G059/JJ17 2G059/JJ22 2G059/KK03 2G059/MM01 2G059/MM08 2G059/MM09 2H040/BA01 2H040 /CA02 2H040/CA11 4C061/CC06 4C061/DD03 4C061/FF46 4C061/FF47 4C061/HH51 4C061/LL01 4C061/WW10 4C061/WW20 5C024/BX02 5C024/CX00 5C024/CY00 5C024/EX41 5C024/EX48 5C024 /EX54 5C024/JX02		
代理人(译)	佐久间刚		
优先权	60/217090 2000-07-10 US		
其他公开文献	JP2004502957A		

**摘要(译)**

提供了一种用于检查样品的表面下微结构的方法和设备。来自多个光学辐射源的辐射沿第一光学路径行进。在第一光路中，装置将来自每个光源的光学辐射聚焦成沿第一光路的多个相应焦点，以提供第一光路的选定部分的基本上连续的覆盖。然后，沿着第一光路的所选部分扫描在延伸到样品中的所选长度内的第一光路上的样品。

