行政院所屬各機關因公出國人員出國報告書

（出國類別： 考 察）

赴歐洲考察儀器技術與產品發展現況
出國報告

服務機關：行政院國家科學委員會精密儀器發展中心
出 國 人：楊宗勳　副研究員
出國地點：瑞士、德國
出國日期：九十年十一月二十日至十二月五日
報告日期：九十一年二月二十六日

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考察儀器技術與產品發展現況

主辦機關:

行政院國家科學委員會精密儀器發展中心

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出國類別: 考察

出國地區: 瑞士　德國

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分類號/目: I0／綜合（科學類）　I0／綜合（科學類）

關鍵詞:

內容摘要: 近幾年來全世界各國無不全力投注在奈米科技的研究發展上，使得奈米科技領域中的研發成果不斷地推陳出新，而且也已成爲我國國家最主要的重點發展科技之一。事實上也開始見到奈米科技在實際生活上的應用，在不久的將來奈米科技、技術一定會爲國家科技界與產業界帶來革命性的重大影響。因此即時掌握世界奈米技術及奈米科技發展的現況，將是帶動國內相關研究之儀器技術與產品發展之重要關鍵。 本中心爲求長期目標的順利達成，同時爲提昇奈米科技相關儀器技術水準，並掌握國際奈米科技產品發展之發展趨勢，以作爲中心計畫執行基礎及未來我國奈米、生醫科技產業技術發展之依據，乃特赴歐洲考察儀器技術與產品發展現況並參與相關會議，以利中心計畫之推行，行程中包括： i.拜訪 Leica 公司共軛焦顯微鏡製造工廠，以充實本中心在共軛焦顯鏡檢測系統、技術之相關儀器技術與產品發展等資訊。 ii.參加歐洲2001奈米科技會議(NanoTech 2001)，瞭解國際在奈米科技領域之研究重點與成果、以及在生物科技方面的相關產品之最新技術趨向。 iii.參訪德國HSG-IMIT微系統公司，進行交流、討論如何利用微系統技術以應用在生醫科技方面的各種課題。除搜集並加強本中心在微系統技術本身的最新產品發展與瞭解之外，而且也希望藉以開展本中心利用已有的微系統技術，跨足生醫科技領域的基礎瞭解。

本文電子檔已上傳至出國報告資訊網

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考察行程表

日期	起	至	工作內容	天次
11/25(日) 11/26(一)	台北 Taipei	瑞士 蒙特魯 Montreux	搭飛機/ 德國法蘭克福轉搭火車	1～2
11/27(二)		瑞士 蒙特魯 Montreux	參加 NanoTech 2001 會議	3
11/28(三)		瑞士 蒙特魯 Montreux	參加 NanoTech 2001 會議	4
11/29(四)		瑞士 蒙特魯 Montreux	參加 NanoTech 2001 會議	5
11/30(五)	瑞士 蒙特魯 Montreux	德國 法蘭克福 Frankfurt	參觀 Leica 顯微鏡工 廠	6
12/01(六)	德國 法蘭克福 Frankfurt	德國 黑森林 VS-Villingen	乘火車/假日撰寫報告	7
12/02(日)		德國 黑森林 VS-Villingen	假日/撰寫報告	8
12/03(一)		德國 黑森林 VS-Villingen	參訪 HSG-IMIT 微系 統公司	9
12/04(二) 12/05(三)	德國 黑森林 VS-Villingen	台北 Taipei	參訪 HSG-IMIT 微系 統公司 /德國法蘭克福 轉機 /回程返國	10 ～ 11

摘 要

近幾年來全世界各國無不全力投注在奈米科技的研究發展上，使得奈米科技領域中的研發成果不斷地推陳出新，而且也已成為我國國家最主要的重點發展科技之一。事實上也開始見到奈米科技在實際生活上的應用，在不久的將來奈米科技、技術一定會為國家科技界與產業界帶來革命性的重大影響。因此即時掌握世界奈米技術及奈米科技發展的現況，將是帶動國內相關研究之儀器技術與產品發展之重要關鍵。

本中心為求長期目標的順利達成，同時為提昇奈米科技相關儀器技術水準，並掌握國際奈米科技產品發展之發展趨勢，以作為中心計畫執行基礎及未來我國奈米、生醫科技產業技術發展之依據，乃特赴歐洲考察儀器技術與產品發展現況並參與相關會議，以利中心計畫之推行，行程中包括：

i. 拜訪 Leica 公司共軛焦顯微鏡製造工廠，以充實本中心在共軛焦顯鏡檢測系統、技術之相關儀器技術與產品發展等資訊。

ii. 參加歐洲 2001 奈米科技會議(NanoTech 2001)，瞭解國際在奈米科技領域之研究重點與成果、以及在生物科技方面的相關產品之最新技術趨向。

iii. 參訪德國 HSG-IMIT 微系統公司，進行交流、討論如何利用微系統技術以應用在生醫科技方面的各種課題。除搜集並加強本中心在微系統技術本身的最新產品發展與瞭解之外，而且也希望藉以開展本中心利用已有的微系統技術，跨足生醫科技領域的基礎瞭解。

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壹、前言

近幾年來全世界各國無不全力投注在奈米科技的研究發展上，使得奈米科技領域中的研發成果不斷地推陳出新，而且也已成為我國國家最主要的重點發展科技之一。事實上也開始見到奈米科技在實際生活上的應用，在不久的將來奈米科技、技術一定會為國家科技界與產業界帶來革命性的重大影響。因此即時掌握世界奈米技術及奈米科技發展的現況，將是帶動國內相關研究之儀器技術與產品發展之重要關鍵。

精密儀器發展中心以累積多年之微系統技術及奈米檢測技術為基礎，配合中心真空技術、光電遙測技術研究的長期發展，亦開始嚐試往生醫科技領域尋求發揮。目前在所規劃的計畫中，即預定有雷射掃描式共軛焦顯微鏡的配置。此目標之達成，有賴對共軛焦顯微術及其相關光學檢測元件等諸多技術經驗之累積。甚且，目前生物科技產業之相關技術及設備的研製與開發，已為世界各國競相發展的重要項目之一，其中必須具有各種微系統技術、光學奈米檢測及設備開發能力。如何將已有的微系統技術、奈米檢測技術，與生物科技互相應用並結合，以產出最大的研究能量，是現今中心長遠發展規畫上的最大課題。因此，確切地瞭解生醫領域中的需求、關鍵問題，才能找出本中心發展最適當的切入點。

本中心為求長期目標的順利達成，同時為提昇奈米科技相關儀器技術水準，並掌握國際奈米科技產品發展之發展趨勢，以作為中心計畫執行基礎及未來我國奈米、生醫科技產業技術發展之依據，乃特赴歐洲考察儀器技術與產品發展現況並參與相關會議，以利中心計畫之推行。

貳、出國目的

◎ 參訪 Leica 公司共軛焦顯微鏡製造工廠，以充實本中心在共軛焦顯鏡檢測系統、技術之相關儀器技術與產品發展等資訊。

共軛焦顯微術為現今生物科技、生醫科技研究之必要技術，位於德國法蘭克福之 Leica 公司素來在光學顯微鏡、光學鏡片、光學照相機等方面的製造極負盛名，而且具多年的產品開發、設計、製造經驗，在共軛焦顯微鏡方面亦有其獨特的技術。此次擬參訪其共軛焦顯微鏡之研發、製造中心，了解其光學設計並討論與本中心現有雷射系統結合等應用問題，以利未來計畫執行之參考。

◎ 參加歐洲 2001 奈米科技會議 (NanoTech 2001)，瞭解國際在奈米科技領域之研究重點與成果、以及在生物科技方面的相關產最新技術趨向。

今年在瑞士蒙特魯 (Montreux, Switzerland)所舉辦之學術研討會 NanoTech 2001 為全歐洲奈米科技的重要國際會議之一，今年為第五屆，此次更將重點著重在微系統與奈米技術在生物科技上的應用與研究，研究人員將匯集在此發表最新之研究成果。欲瞭解當今奈米科技與生醫技術應用之研究重點與成果，參加 NanoTech 2001 學術研討會可說是最佳的途徑。

◎ 參訪德國 HSG-IMIT 微系統公司，進行交流、討論如何利用微系統技術以應用在生醫科技方面的各種課題。除搜集並加強本中心在微系統技術本身的最新產品發展與瞭解之外，而且也希望藉以開展本中心利用已有的微系統技術，跨足生醫科技領域的基礎瞭解。

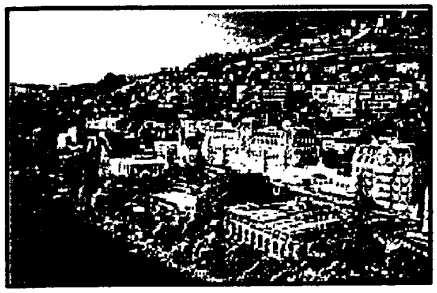
德國 HSG-IMIT 微系統公司近年來，對於利用微系統技術以開發生醫領域之各項應用，成績卓著。此次考察行程中特別安排參訪 HSG-IMIT 微系統公司，將針對「微系統技術在生醫工程上的應用」、「封裝程序、技術」、「從研發到商品化之路」、「生醫應用上的實際問題」、「應用領域」等課題，分別進行交流、討論，藉此經驗分享，必有助於未來中心相關計劃之執行。

參、參訪過程

(一)、 參加第五屆 NanoTech 2001 國際會議：

考察行程第一站是參加第五屆 NanoTech 2001 國際會議，此項會議的舉辦地點一直都是在位於瑞士蒙特魯市(Montreux) 的 Montreux Palace Hotel 內舉行，在三天的會議議程中，來自美、歐各國的專家學者各就其研究成果做詳盡的報告，所報告的主題全圍繞著微奈米技術在生物科技上的應用與研究，概括而言就是如何做到奈米級分子的操控與量測。其中更不乏令人驚奇、讚嘆的異想與研究方法。

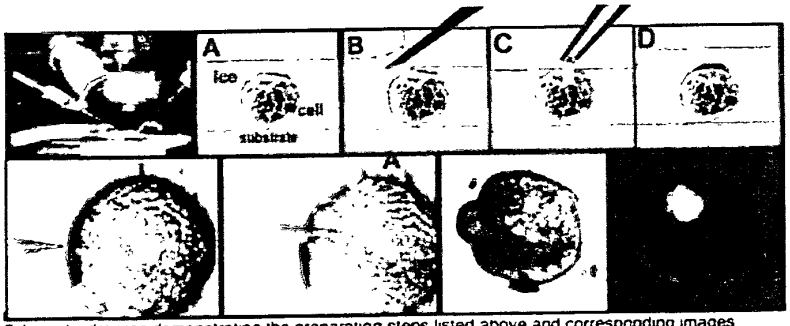
全部參加會議的人員，大約在 150 人左右，利用廠商參展和壁報討論的時段，差不多可以和一半以上的參加者打招呼、交換名片。尤其是一位來自日本的副教授，他利用超音波來操控分子的技術頗負盛名，知道我是唯一來自台灣的參與者，一直向其他人介紹台灣的半導體製造技術獨步全球，是用來發展奈米科技最佳的基礎，還頻頻要求日後保持聯繫，尋求可能的合作機會。讓我因為國內半導體、電子業界在國際上的成功，而與有榮焉。



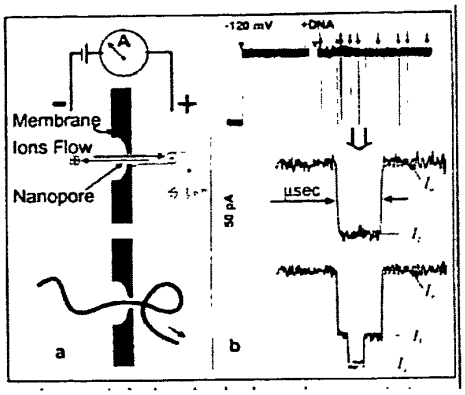
瑞士蒙特魯市與 Montreux Palace Hotel。

其中在會議中由大會邀請的演講者 Prof. Gunter R Fuhr (Humboldt University, Germany)，發表對細胞顯微手術的技術，已發展到在低溫下(-10°C～-150°C)可以將單一細胞利用

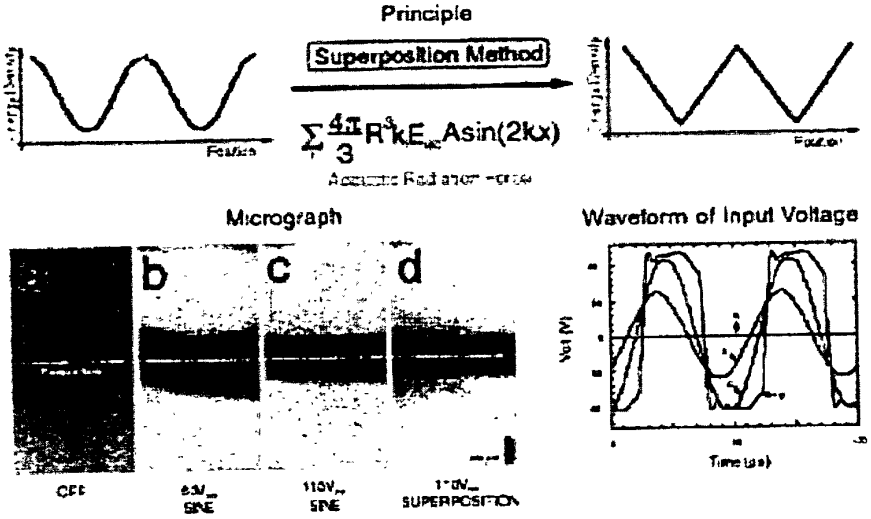
顯微手術切開，放入螢光奈米粒子，再將接合回原來的的細胞，而且手術過後的細胞還可以神奇地維持正常地活動。Prof. Andreas Manz (Imperial college of Science Technology and Medicine, UK) 則發表如何改進螢光顯示技術，以大大地改進其應用上的極限。另外，Prof. Daniel Branton (Harvard University, USA) 更是提出 DNA 定序的新奇方法，利用由奈米孔洞所連通的化學溶液，DNA 在溶液中流過此奈米孔洞時，依其接觸的鹼基不同，而使得所量測的電流大小產生變化，雖然此電流量非常小(~pA)，而且訊噪比亦極小，如何發展出精密電流量測儀器將可以有效地幫助解決此新方法的實現，如此也將全新地改變 DNA 的分析方式，潛力很大。Dr. Marc Madou (Nanogen Inc., USA) 也在會議中提出在 21 世紀中生物科技的可能發展趨勢，他認為未來生物科技應該結合 top-down 以及 bottom-up 二種方式進行發展，同時也期望仿生科技(biomimetics)的發揚，“Mimic to the nature usually fails, but new working technology will be resulted and developed.”



Schematic drawing demonstrating the preparation steps listed above and corresponding images below. Shown is an egg cell of *Ophryotrocha puerilis*, diameter around 100 µm. A) Preparation of the cell surface, B) Opening of the cell envelope under nitrogen atmosphere, C) Insertion of a fluorescent nanobead, D) Closing the cell wounding and view after defrosting in suspension



除了在生物技術方面的應用之外，奈米科技的發展也是議程的重點之一。其中以 Prof. Kenji Yasuda (University of



Tokyo, Japan) 的研究成果最為卓著，在報告中利用超音波的輔助，能達到對 DNA 等奈米級分子聚集、分離、混合的各種操控能力，下一步極有潛力發展出新式的奈米科技操控儀器。

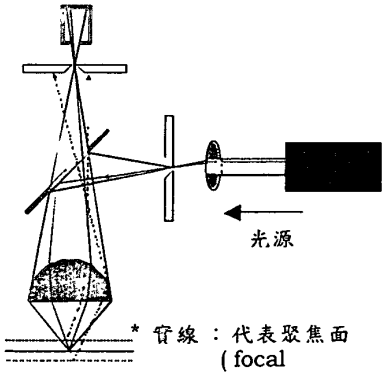
此外，大會亦結合歐洲許多著名的生技公司展出其產品，並且提供不少的面對面討論場合，以增加雙向溝通的機會。由此也瞭解到現今生物技術在商業生產上的發展狀況。(見附件)

(二)、 參訪 Leica 公司共軛焦顯微鏡製造工廠

第二站由瑞士蒙特魯轉搭四班歐鐵火車，來到德國法蘭克福的近郊參觀 Leica microsystems 公司。Leica 公司在全歐的分公司很多，而在此的分公司則主要專注在各式共軛焦顯微鏡的研發與製造。透過台灣代理商的引介，全程都由分公司副總裁陪同介紹，不僅實地參觀全公司各部門的運作情形，而且也針對感到興趣的機型，詳細地詢問各項細節。雖貴為副總裁，但是對於技術上的問題，仍然知之甚詳，能夠針對問題對答如流，因此對於共軛焦顯微鏡有了更進一步的瞭解。

Dr. Martin Hoppe, Vice President Marketing/Sales of Leica Microsystems

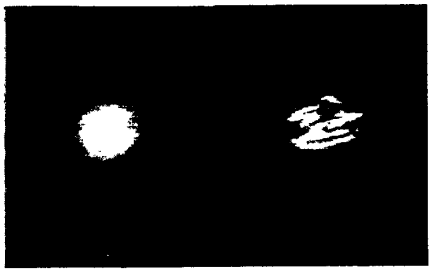
- 共軛焦點呈像技術



當光聚焦於樣品上，其聚焦點的斷層面，我們稱為聚焦面 (focus plane)。聚焦點外的樣品層，則稱為非聚焦面 (Out-of focus plane)。利用通過光學針孔光圈 (Pinhole) 蒐集來自樣品聚焦面的光所行成的影像，將非同一聚焦面的光排除於光學針孔光圈外 (如為擷取影像之黑色背景)，所形成的影像，我們簡單的稱為共軛焦點 (焦距) 影像 (Confocal Image)。

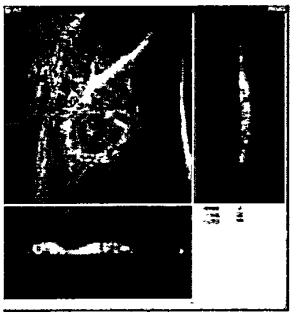
一般，在顯微鏡下所觀察的影像，都有來自聚焦面（Focal plane）及 非聚焦面（Out-of focal plane）的光，故所提供的影像品質解析較差，也無法一層一層的深入樣品作顯微觀察。

共軛焦技術去除傳統顯微鏡影像的迷光（Stray light）能提供更高的光學解析，提供更佳的 axial 及 lateral 解析（Point Spread function）。



左圖示：傳統顯微鏡的螢光影像。右圖示：共軛焦顯微鏡的螢光影像。其消除了非聚焦面的光，故呈像對比清晰，光學解析高。可真正清晰的作顯微結構的觀察。

在醫院，我們都知道電腦斷層掃描技術 (CT) 能提供 3D 立體的斷層掃描，能對全身作立體斷層掃描，使我們能清楚的看到身體內部某一部位或某一斷層面的組織結構。 顯微鏡的共軛焦呈像技術也有類似的功能。能提供樣品顯微結構的立體掃描，光學斷層連續掃描。此外，多重螢光與螢光離子流的定量分析更是此種技術的使用效益。應用顯微鏡的共軛焦呈像技術，使用人員可任意 依照樣品的厚度，指定樣品的上下點位置，設定每一光學切片的厚度，做連續的光學斷層掃描。最後，可重組為一個立體影像，連續式的 3D 電影放映，也可作各種角度的旋轉或切面觀察。 如為螢光離子流的定量分析應用，更可取得 3D 的離子流分佈。

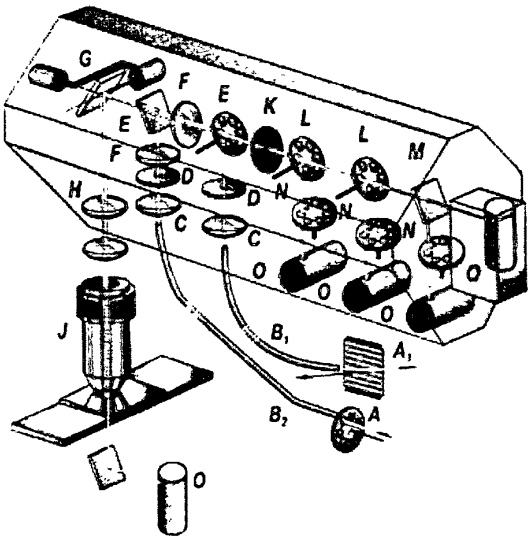


雷射掃描共軛焦顯微鏡可在一個受檢樣品同時取得多種超高解析的螢光影像（如 FITC、TRITC、CY5、DAPI、並重疊在 DIC 影像）開拓了研究視野。在傳統顯微鏡的應用裡，使用人員必須重覆照相或個別旋轉更換螢光濾鏡，才可取得解析極為有限的螢光影像。而且，無法瞭解其立體內部結構。

近代的 雷射掃描共軛焦顯微鏡 主要組成包括下列組配：

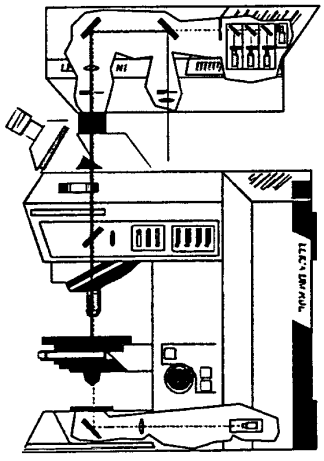
1. 雷射光源 (Laser illumination sources)
2. 顯微鏡 (Microscope)
3. 共軛焦掃描器 (Confocal Scanner)
4. 電腦操控工作站 (Control workstation)
5. 應用軟體 (Application Software)

- 共軛焦掃描器光路圖



傳統的濾鏡式共軛焦掃描器的雷射光源 (UV-laser，VIS-laser，IR-laser) 可經由濾鏡 (A：ND Filter) 或 超音波光學調變系統 (A1：Acousto Optical Tunable Filter。AOTF) 來選取雷射激發光之波長及調整所選用波長的雷射光強度，然後，通過光纖 (B1：可見光雷射或多光子紅外光雷射使用之光纖，B2：紫外光雷射使用之光纖) 傳導至共軛焦掃描器。由一個極為精密的聚光鏡 (C : Focusing Lens)，將雷射光束聚焦通過單一的激發光針孔 (D : Excitation Illumination Pinhole)，然而，紫外光雷射

尚需配合所使用的物鏡倍率來選用特定的針孔鏡 (F : UV Pinhole Lens)，以便將紫外光雷射穩定的平行導入分光鏡 (E : Beam splitter)。分光鏡會將特定波長的光反射至共軛焦 XY 掃描鏡 (G : Galvanometer-Driven Single XY Scanning Mirror)，經由 XY 掃描鏡所掃描產生的光會通過一組特殊的聚光鏡 (H : Lens) 及 鏡頭 (J : Objectives) 以聚焦至樣品，在樣品上作 X-Y 掃描。 同時再經由縱深掃描載物台 (Galvanometer Z-stage) 的同步縱深上下的顯微移動，即構成了 XYZ 三維立體的連續掃描。 來自樣品的反射螢光，經由鏡頭收集螢光光子，只有來自樣品聚焦面的螢光可以通過單一個感測光針孔 (K : Detection Pinhole)，其餘非聚焦面的反射光則被阻擋濾除，呈像為黑色的背景。 通過單一個感測光針孔分別導入至(最多) 4 個 PMT 光電感測器 (O : Photomultiplier)，在每個感測器之前，各有一組濾鏡飛輪 (N : Filter wheel for Emission Filter)，可裝入所要感測的螢光光譜的篩選濾鏡 (如 Long-pass 510nm，Band-pass 450 – 490，Short-pass : 510 nm)。



所謂 4 -channel 即表示掃描器裝有 4 個 PMT，並可同時感測擷取 4 組螢光訊號。 然而，穿透光影像，則可直接由一組安裝於顯微鏡聚光鏡下的 PMT 來感測，如 相位差 (PH) 或 微分干涉 (DIC) 穿透光影像。以便和 4 個螢光影像做重疊觀察。(Overlay)，可提供螢光原位 (colocalization) 訊息。 此 PMT 安裝於顯微鏡內，其光路並無通過共軛焦針孔，僅為一般的穿透光影像。其可同時掃描感測 5 個 PMT 的影像。

- 共軛焦系統適用的雷射光源

1. 可見光雷射光源 (Visible Laser)：

A).離子雷射

- Ar-Kr Laser : 476, 488, 568, 647 nm.
- Ar laser : 458, 476, 488, 514 nm.
- Kr Laser : 568 nm (Yellow).
- Kr laser : 647 nm (Red)
- Kr laser : 752 nm (Near IR)

B).氦氖雷射 (He-Ne laser)

- He-Ne laser : 543 nm (Green)
- He-Ne laser : 594 nm (Yellow)
- He-Ne laser : 612 nm (Orange)
- He-Ne laser : 633 nm (Red)
- He-Ne laser : 1523 nm (Near IR)

C). 二極體雷射 (Diode-Pumped Solid-State laser , DPSS)：

- Diode Laser (635 nm) 低功率的二極體雷射.
- Diode-Pumped Solid-State Laser (DPSS 532 nm Green)

2. 紫外光雷射光源 (UV Laser)：

A). 氦鎘雷射

- He-Cd Laser : 354, 442 nm.

B). 氬離子紫外光雷射

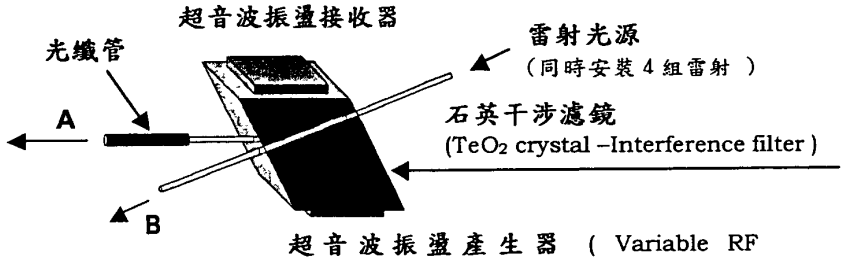
- Ar-UV Laser : 351, 364 nm.

3. 紅外光雷射光源 (IR Laser)：

- Ti-sapphire Ultrafast laser : 690 – 1050 nm.
  此類雷射應用於多光子影像擷取應用，在脈衝速率上有 femto-second 及 Pico-second 之分。

雷射的選用視所擬使用的螢光染劑而定。研究人員可嚐試不同的雷射作為激發光源，然而，雷射強度的調整也極為重要。故使用人員可選用 Neutral-Density Filter 或 AOTF (Acoustic Optical Tunable Filter) 來調控衰減強度，以避免螢光的快速漂白，或者，避免高能量的雷射光造成樣品的光傷害。其中 ND 濾鏡提供固定的能量衰減，如 20%，50%，75% .. 等。然而，AOTF 可利用振盪頻率來篩選指定所須

的雷射波長，並可針對所選定的波長作 0% - 100% 的連續調整，以正確的掌握所須雷射強度，即適當的控制激發光源的強度。 激發光源的強度的控制應該要足以激發染劑但又不會傷及樣品，應調控至避免螢光染劑的快速漂白，而且，要避免染劑間的光譜交互重疊。AOTF 不僅用以激發強度調整應用，更可有效的應用於 FRAP (Fluorescence Recovery



< AOTF 圖示 > AOTF 可以微秒間距切換所須的雷射波長，也可同時讓數個波長的雷射光通過。

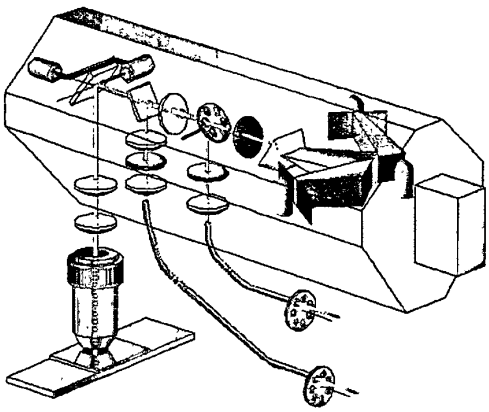
After Photo-Bleaching)。

指定的振盪頻率 RF，可指定所須的雷射波長。 唯有此波長可通過光纖 (A) 傳導入顯微鏡，非此頻率的波長，則被折射阻擋 (B) 利用其振盪頻率的振幅大小，改變晶體的角度，可控制雷射的強度。目前的共軛焦系統已可同時調控 8 條波長的雷射光。

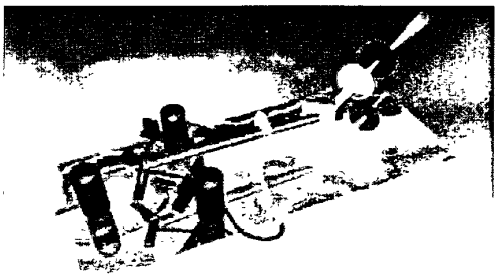
- 新一代的雷射掃描共軛焦分光光譜顯微鏡

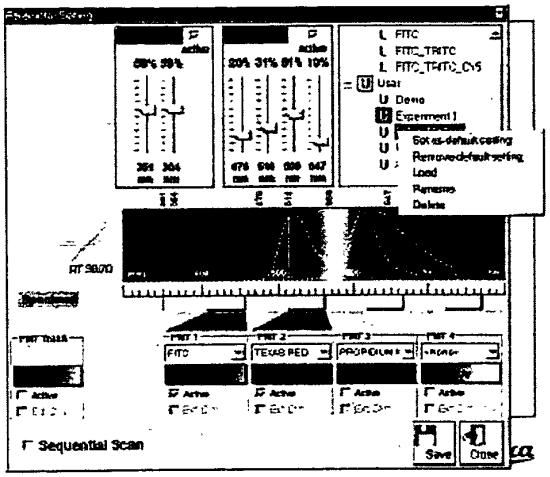
面對各式各樣的應用，各式各樣的螢光染劑及其不同的使用條件，在傳統的濾鏡式共軛焦系統 (Filter-based)，僅能使用為數有限的螢光濾鏡 (例如 6－8 個)，而且又是波幅極寬的固定式濾鏡，濾鏡又往往造成螢光訊號的嚴重折損，所以難以發揮使用效益。 此外，許多新一代的染劑，都有新發現的波長，傳統的濾鏡式共軛焦系統難以應用的上，如要更換濾鏡，調整校準工作更是難以掌握，費時費力。也有些螢光染劑會因條件的不同，如濃度，酸鹼值，而有所移位

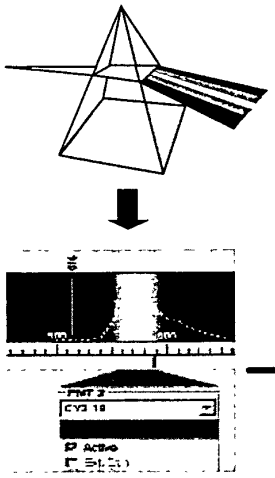
(shift)。當面對新一代的各種螢光蛋白時 (GFP)，其激發光譜與螢光釋放光譜都很接近，彼此交互重疊情況極為普遍與嚴重。要克服此感測技術屏阱，分光光譜式的感測技術是目前最佳的解決技術。



新一代的共軛焦系統，是將通過感測光針孔的反射螢光，經過一組特製的菱鏡 (Prism) 產生連續的光譜 (螢光釋放光譜)。 其可感測的光譜範圍廣達 400 – 850 nm 間。 此設計替代了傳統的濾鏡及分光鏡。 因為，光通過濾鏡的數目減少，其光學穿透有效率更高，影像更為鮮明，解析更高。 平均來自樣品的反射螢光到達感測器時，仍能提供 90% 以上的穿透率。 (Optical Transfer Efficiency)





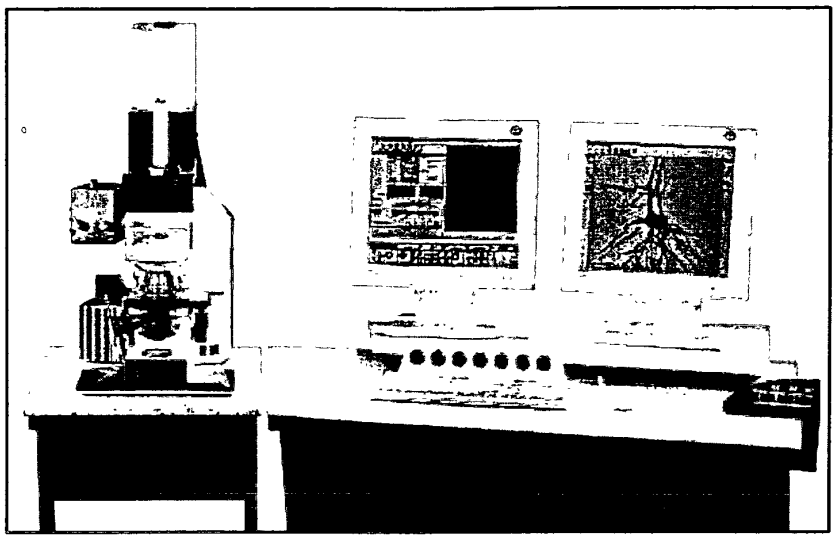


光譜式分光感測技術，可讓所有螢光光譜都能夠100% 的感測擷取，無任何損失.

光柵（Slit）：
位於每一個 PMT 之前，取代螢光濾鏡與分光鏡.可任意移位，可任意移動柵門寬度，即自行設定取決光譜範圍

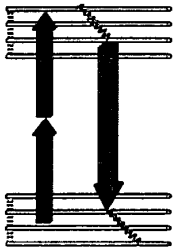
光譜操控圖示。

在掃描器內的 4 個感測器之前，各有一組光譜調控柵門，此柵門即控制感測光譜通過的波長範圍。(傳統濾鏡式的系統，僅能使用少數的固定波段的濾鏡來篩選感測光譜) 只要調控此柵門的間距，即可輕易的調整感測光譜範圍。即是自行設計出無限的感測光濾鏡。使用人員，也可反過來，指定某一光譜範圍，供其自動掃描感測，如 490 – 550 nm，每一 step 為 2 nm。 所以，應用此技術，能真正的掌握每一螢光染劑的釋放光譜，避免螢光交互重疊 (crosstalk)，也避免螢光漂白。此技術也是唯一可作多重螢光的全光譜感測與呈像。 例如，當您使用 GFP. BFP, YFP, ECFP 或 DsRed 時，完全可輕易的清楚將螢光顏色分離顯示。



TCS SP2 雷射掃描共軛焦光譜顯微鏡系統

- 雷射掃描共軛焦多光子(雙光子)影像技術
  (Multi-Photon Imaging)



2 photon excitation

Principle of Two Photon Microscopy

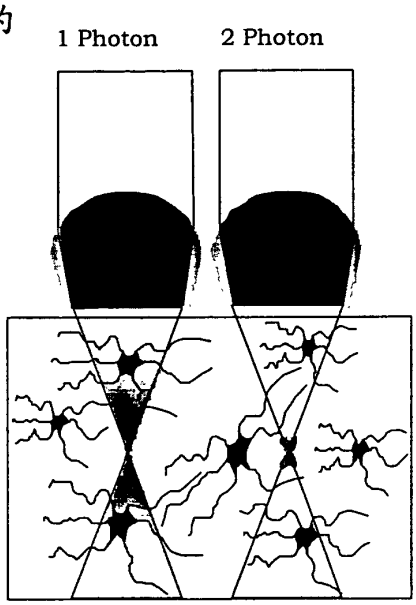
simultaneous absoption of 2 photons for excitation a fluorochrome with the half energy (= double wavelength)

在雷射掃描共軛焦顯微鏡的應用裡，一般都必須使用高能量（較短波長）激發光源來激發螢光染劑，因為此高能量才足以改變分子能階，並在回到穩態時釋出較長波長的螢光。所以，一般光源都使用高能量的單光子（Single-Photon）可見光雷射（Ar-Kr/ He-Ne Laser）或紫外光雷射（Ar-UV Laser）。

然而，螢光染劑的分子本身並不管此激發能量是否來自單光子，雙光子或更多的光子所攜帶的能量。只要能量足夠

改變基態能階即可。如果，激發光源的光子俱有 2 倍的波長，則其光子僅有其一半的能量，並不足以激發螢光染劑。

然而，如果同時使用 2 個以上的雙倍波長光子的能量，以能量相加的交互共同方式，來激發螢光染劑，則此共同的能量，就如同單光子的能量，足以改變能階，並促使螢光染劑釋出與單光子激發後所產生的相同波長的螢光。 此即表示雙光子技術。例如，DAPI 的 Ex : 359 nm，Em : 461 nm，我們可使用單光子雷射 Ar-UV laser (約 351 nm) 來激發，也可使用雙光子雷射 Ti-Sapphire (約 702 nm) 來激發，同樣可得到相同波長 461 nm 的螢光。



雙光子雷射掃描所產生的螢光影像都發生在樣品的聚焦面的雷射聚焦點

一般的單光子雷射聚焦點則會影響樣品面積較寬深的部位。雙光子螢光影像已經是可謂是“完全聚焦點”，不是大面積樣品的影光影像。故此聚焦點的反射螢光光路無須經過共軛焦掃描器內的感測光針孔 (Detection Pinhole)，可 100% 的直接於安裝在顯微鏡內的 Non-Descanned Fluorescence Detector 所感測。所以，雙光子螢光影像並非共軛焦影像，是屬於樣品焦點的直接螢光影像。同理，如果同時使用更多個光子共同來激發螢光染劑，使其產生與單光子激發後所產生的相同波長的螢光，此即表示多光子技術。

然而，兩個長波長的光子以上的共同交互合作激發機制，必須在極短的次微秒時間內完成，所以才有 Pico-second (10^{-12} sec) 及 femto second (10^{-15} sec) 技術。

- 為何要使用雙光子雷射掃描影像技術 ？

  ✓可依應用做適度的取代紫外光雷射 (UV)。

  ✓紫外光雷射為單光子，造價昂貴。

  ✓因光傷害問題，無法使用於活體細胞。

  ✓許多螢光染劑都使用較短波長的紫外光來當作激發光源，因其激發能量較高。然而，紫外光極易散射 (high UV-scattering)，傳輸與穿透不易，所以必須使用特別製作的光學元件(造價極為昂貴，品質不易控制)。

  ✓紫外光極易散射，會沉降在樣品的表面層，就如同晒傷，會致使樣品的熱傷害。 紫外光的輻射，會致使毒害，致使 DNA 傷害。

  ✓增加取樣的深度，能更深入樣品裡層。

  ✓不會產生光毒傷害。

  ✓減低螢光漂白的速率，增加螢光觀察與掃描時間。

  ✓使用多種染劑時，呈像無色差現象。

  ✓較容易將激發光與釋出光的波長分開，螢光影像比較不會有重疊現像(cross-talk)。

  ✓無須感測光針孔，所以反射螢光可 100%的被感測。

  ✓可使用絕大部份的螢光染劑，尤其，是須使用紫外光光源所激發的雷射。

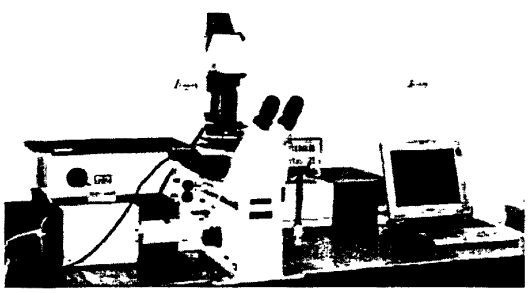
  ✓可使用於活體細胞，而不會造成傷害。

  ✓有效的應用於胞外或胞內離子流定量分析及螢光影像。

  ✓適用長時間影像擷取記錄。

- 雙光子與單光子雷射掃描影像技術的優劣點分析 ？

使用效益的優劣點分析	雙光子	單光子
光學解析	較差	最好
取樣深度	較深	較淺
活體細胞組織之應用 (螢光離子流影像擷取與定量分析)	較好	尚好



＊ 資料來源：“徠卡　雷射掃描共軛焦顯微鏡之技術與應用概論”

(三)、 參訪德國 HSG-IMIT 微系統公司：

最後一站來到德國黑森林 Villingen-Schweningen，位在城郊的 HSG-IMIT 公司，是一家以微系統技術製造見長的公司，與瑞士微系統技術基金會長期合作舉辦許多的短期課程。這次剛好能參與其中的生醫相關應用課程，包含「微系統技術在生醫工程上的應用」、「封裝程序、技術」、「從研發到商品化之路」、「生醫應用上的實際問題」、「應用領域」等課題，分別進行交流、討論。

主講人對於仿生科技(Biomimetics) 涵養極深，在討論交流當中舉出了不少仿生科技開發成功的技術研發案例，深入淺出的介紹，不禁覺得儘管上帝造萬物的神奇，人類終究可以開始稍稍一探其中奧妙；也因此更體會到，人類最終的敵人就在於人類自己。不少的開發案例，最後都因為 FDA 標準嚴格地長期審核、市場行銷策略等人為因素的影響而夭折，無法問世。

其中除了對 FDA 審核標準的申請流程，讓每一位參與者都能有清楚而深刻的瞭解之外，所舉出的一個耳朵助聽器的技術開發過程，從仿生科技對耳朵功能性的細部瞭解起(光是這一部份，就讓人覺得其中所牽涉技術的複雜，以及上帝造物的神奇)，再到人工耳朵的仿製過程上工程技術的艱難、創意上的克服等，最後雖然成功地開發出一功能性高的產品，卻因 FDA 審核的長期拖延而失去上市的機會。一方面也許 FDA 審核標準、流程需要因應新科技而修改，但是反過頭來想，任一項的產品的問世，還是需要經過重重難關的考驗，通過之後才能算是真正的成功產品。

肆、達成之任務

1. 參加歐洲 2001 奈米科技會議 (NanoTech 2001)，以瞭解國際在奈米科技領域之研究重點與成果、以及在生物科技方面相關產品的最新技術趨向。藉由參與此會議的過程，瞭解到目前先進奈米科技研究程以及生物科技方面的發展。

   從研討會中可看出生物晶片、生醫檢測儀器等是現今歐洲的研究主流，也是投入相當多人力與資源的領域，顯示目前他們在奈米生物研發方面的努力是非常值得我們借鏡的。而且已有不少商業公司產出各式的生技產品，由此可見在奈米、生物科技方面的研發競爭是非常激烈的，有時間上亦是具有相當的急迫性。

   如何利用此行所收集到的相關資料，進而在中心內部如何調整人力與資源，並全力趕上此研發趨勢，將是下一步必須思考的重點所在。

2. 拜訪 Leica 公司共軛焦顯微鏡製造工廠，從公司管理與運作方式、技術發展策略、製造生產作業等，詳細地瞭解國際一流生產公司的營運方式。相關的共軛焦顯微術、雙光子或多光子顯影技術等是目前生物技術之生物晶片平台中，極先進且重要技術，非常值得進一步建立其相關研發能量。而且透過關鍵技術的資料收集與面對面溝通瞭解，擴展並充實本中心在共軛焦顯鏡檢測系統、技術之相關儀器技術與產品發展等資訊。

3. 參訪德國 HSG-IMIT 微系統公司，進行交流、討論如何利用微系統技術以應用在生醫科技方面的各種課題。除搜集並加強本中心在微系統技術相關應用的最新產品發展與瞭解之外，而且也希望藉以開展本中心利用已有的微系統技術，跨足生醫科技領域的基礎瞭解。參訪中得知除瞭解該單位對於

微系統製程設備發展之過程與技術外，亦蒐集其微系統製程設備之技術及研發之成果資料，並可作為中心在此一領域技術發展方向的參考，以提升中心在微系統技術的研發能力，並進而開發在生物科技領域的相關應用，確定下一技術研發的方向。

伍、心得與建議

這次出國能夠圓滿達成任務，端賴許多同事經驗的傳授以及相關人員的協助，才能做好事前的周密計畫，並且帶回了許多豐富的資料，經過整理後提出一些心得與建議如下，期能作為參考：

一、在瑞士蒙特魯參與 NanoTech 2001 會議議程期間，深覺主辦單位在設計議程上的用心。所邀請來的演講者均是一時之選，除了在研究專業領域上各有擅長，而且在演講內容與技巧上想必也都經過一番的排練。因此，幾天下來儘管數十場的演講份量相當重，但是一場接著一場都是思想上不同的衝擊，稱得上是豐富的知識享宴。透過純熟的講演技巧，每位演講者都能將充實、創新的研究成果傳達給每位在場聆聽的聽眾，也因此在休息期間參與者之間更能產生共鳴，引起非常熱烈的討論，達到會議的最終目的。在此建議往後能將此項會議列入出國考察的重點項目，以主辦單位的自我期許程度，此項會議也成為歐洲地區重要的國際會議之一，非常值得參與。

二、在參觀德國 Leica 公司共軛焦顯微鏡製造工廠時，深切地感受到歐洲濃厚的人文氣息。儘管是民營的營利機構，但是對員工的管理方式，卻是極為人性化管理的。除了因為辦公室的個人化設計，讓每位員工有各自的隱密空間，可以專心工作之外，Leica 公司更允許員工上班時間的自我管理，不需要藉由上班打卡來管制員工的出勤狀況，讓員工可以自我調整最佳狀況出勤，以激發出更有效的工作效率。

因此，在參觀過程中繞遍了公司上上下下，以下午的上班時間卻看不到多少人，除了空間的隱密性設計，提供員工能夠專心工作的優良環境之外，錯過了部份人的上班時段

也是原因之一。經過解釋，才瞭解員工之間已經發展出一套上班時段的模式，例如生產線上的員工多傾向一大早來上班，然後中午過後三、四點就陸續離開，可以更方便地照顧家庭；研發人員則是偏向十點過後上班，晚上七、八點後才會下班；至於程式軟體開發人員則算是最特殊的，因為多半在半夜才有最好的程式設計效率，因此在白天經常是看不到人的。儘管這樣的方式在內部管理上，增加許多困難度，但是 Leica 寧願犧牲管理上的複雜度，來更體貼地配合員工的個人獨特性，願意以激發員工的工作效率為主要考量，而不是以管理方便為目的。而這樣應該也算是 Leica 公司能在國際間嚴峻的競爭現實下，依然立於領導地位而不墜的原因之一。

反觀國內，也有許多民間公司已經成立“人力資源部門”，慢慢地把員工管理朝向更人性化的管理，對公司來說也算是更進步、更有效率的投資與管理。

三、 以德國 HSG-IMIT 微系統公司的營運方式，企業主願意提供空間與時段，以提供研發的交流機會，不儘對企業本身的文化有提昇作用，而且藉由交流帶來的觀念上衝擊，更可能讓企業隨時保持向上的競爭力。因此，在中心內部不僅應該需要開拓與學界、業界更多、更廣的交流合作機會，同時也應該藉由各種交流的機會，改善本身不足之處，以增加中心的競爭力。

陸、結語

此行在參加國際研討會以及參訪公司的行程中，得到了些許寶貴意見，和各國學者交換彼此經驗後，更是發現目前的大環境已經是奈米科技與生物科技發展的開端，其融合的領域相當廣泛，包括機械、電子、化工、材料、量測、生物、醫藥等，許多的相關技術正被積極而且急速地開發當中，具有相當寬廣的發揮空間，非常值得中心作為規劃未來發展方向之參考。

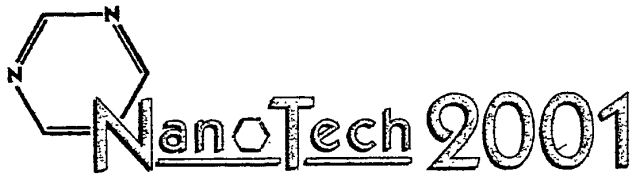
柒、附件

一、 參加第五屆歐洲2001奈米科技會議 (NanoTech 2001) 相關參考文件

二、 德國 Leica 公司相關資料

三、 參訪德國 HSG-IMIT 微系統公司之相關資料

附件一、 參加第五屆歐洲 2001 奈米科技會議 (NanoTech 2001)相關參考文件



Final Program

The 5th Annual European Conference on Micro & Nanoscale Technologies for the Biosciences
November 27 - 29

Short Course On Microsystems Technology
November 25 –2

Montreux Palace Hotel, Switzerland

[redacted]

Agilent Technologies

evotec OAI

EUROPRACTICE
BASIC SERVICES

[redacted]

SCITEC
Science & Technology

FOREWORD

Welcome to NanoTech 2001 in Montreux

When it meets in Montreux, Switzerland, November 27-29, the fifth edition of the European Conference on Micro and Nanoscale Technologies for the Biosciences will showcase the same kind of innovative and fascinating work in the field that made the first editions such a success.

NanoTech 2001 in the midst of a Center of Excellence.
Together with leading European research institutions and companies from Europe and USA, NanoTech 2001 will take advantage of the proximity of the centers of excellence in microsystems technology – the *Swiss Federal Institute of Techology* (EPFL) in Lausanne, the *Institute of Microtechnology* (IMT) in Neuchâtel, the *Swiss Center for Microelectronics and Microtechnology* (CSEM), and their applications to the biosciences with leading experts from European countries, North America, Japan and Korea.

A Full Program

NanoTech 2001 will above all be a forum where participants can meet and interact in a variety of contexts. The three-day program, in addition to the regular sessions of the conference on Tuesday, November 27 through Thursday, November 29, will involve poster sessions, sessions of commercial "snapshot" presentations (10-minute *précis* of participating companies' products and services), a robust exhibition of companies and academic institutions, industry-sponsored meetings on Wednesday evening.

PEOPLE

Scientific Committee

Philippe Renaud, EPFL, Switzerland, Program Chairman
Albert van den Berg, University of Twente, The Netherlands
Andrea Chow, Caliper Technologies, USA
Günther Fuhr, Humboldt University, Germany
Marc Madou, Ohio State University, USA
Andreas Manz, Imperial College of Science, United Kingdom
Staffan Nilsson, University of Lund, Sweden
Sabeth Verpoorte, IMT, Neuchâtel, Switzerland

Organizers

Alain Donzel, Conference Organizer

Scitec Conference Coordination Office
Av. de Provence 20
CH-1000 Lausanne 20
Switzerland

Phone: +41 21 624 15 33, Fax: +41 21 624 15 49
E-mail: symposia@ip-worldcom.ch
URL: http://www.nanotech2001.com

Key to Badges

White: Delegates & Presenters
Gold: Scientific Committee & Organizers
Blue: Exhibition Personnel
Blue / red: Press Pass

GENERAL INFORMATION

On-Site Registration Desk

All registrants must check in at the registration desk located at the main entrance of the Petit Palais of the Montreux Palace Hotel. The registration desk will be open for the duration of the short course and regular program, beginning with course registration at 14.00 on Sunday, November 25. To reach the registration desk during the event, call +41 21 962 12 70 or fax to +41 21 962 19 41.

Language

All oral and poster presentations will be given in English; there will be no simultaneous translation.

Social Program

In addition to the regularly scheduled coffee breaks, the social program of **NanoTech 2001** will include a reception on Tuesday evening, November 27, in the exhibition hall from the close of the afternoon session to 19.30, and a banquet dinner at the Palace Hotel, beginning at 20.00. A dinner ticket is provided to all regular delegates; additional tickets can be purchased at the registration desk for CHF 90.00 each.

Short-course registrants are invited to participate in a wine-tasting excursion to the Château du Châtelard in Montreux. The bus will depart from in front of the Palace Hotel at 18.30 on Sunday, November 25, and will return participants to the Hotel at 20.30 that evening.

Dining in Montreux

For dining options, we can suggest the following restaurants in Montreux:

Café-Restaurant et Caveau des Vignerons
Rue Industrielle 30 bis
phone: 963 25 70
Traditional Swiss fare: diverse fondues, raclette, etc.

La Couronne (or) **Le Brigantino**
Avenue des Alpes 102
Italian food for any budget, just above the Palace Hotel.

Brasserie Le Guignard
Montreux Palace Hotel
Varied international cuisine.

Han (Casino de Montreux)
Rue du Théâtre 9
phone: 962 83 83
Asian cuisine: Mongolian Barbecue.

La Rouvenaz
Rue du Marché 1
phone: 963 27 36
Pizzeria with jazzy atmosphere.

La Terrasse (Hôtel Eden au Lac)
Rue du Théatre 11
phone: 963 55 51
French cuisine on the lake.

EVOTEC COURSE

evotec OAI

November 26, 2001 (afternoon session)

Quantification of Biomolecular Interactions in Nanostructures with Single Molecule Resolution

Target Audience

The course is aimed at scientists and scientific related management in the pharmaceutical, biotechnology and related life science industry as well as academia. It will give an introductory overview of recent advances and future trends in the field of single molecule detection technologies and their biological applications. Course participants will be granted a 10% discount on the NanoTech 2001 registration fee, however extra on site expenses incurred through the extra day's stay must be covered by the participant.

Course Instructors

Prof. Dr. Claus A. M. Seidel, Max-Planck-Institute for Biophysical Chemistry, Göttingen, Germany.
PD Dr. Jörg Enderlein, Institute of Physical Chemistry, University of Regensburg, Germany.
Dr. Peet Kask, Evotec OAI and Institute of Experimental Biology, Harku, Estonia.
Dr. Leif Brand, Evotec OAI, Hamburg, Germany.

Course Outline

The inclusion of nanostructure carrier systems into a wide range of life science applications places new demands on novel detection technologies which must give access to high content data down to the molecular level and additionally be insensitive to miniaturisation.

Recent advances in modern fluorescence spectroscopy have made it possible to study biomolecular interactions down to the single molecule level in a time resolved manner with high statistical accuracy. Different methods of analysis have been developed recently to exploit the power of these measurement techniques, thus revealing detailed information about individual molecules, different molecular species and their reaction pathways in a heterogeneous sample. Highly sophisticated multiparameter analysis methods are capable of simultaneously evaluating fluorescence signals from single molecules taking part in biological interactions on the basis of changes in their fluorescence lifetime, molecular brightness, anisotropy, spectral shift or on the basis of transferred fluorescence resonance energy transfer.

Conformational and structural dynamics of individual molecules, mechanistic intra- and intermolecular studies and quantitative analysis of diverse biomolecular assay systems including single cell microchip applications will be presented in order to demonstrate the outstanding power of single molecule detection technologies. Novel design strategies of optimised fluorescent tags that take advantage of micro-environmental effects will be illustrated by the interactions of fluorophores with metal coated nanocavities.

SHORT COURSE

Course Description

Microfluidic systems, fabricated using technologies adopted from the microelectronics industry, are enabling researchers from many disciplines to approach their activities in new ways. Chemical analysis in particular has benefited from this trend, with demonstration of performance enhancement for techniques like capillary electrophoresis in chemically etched microchannel manifolds. Ultimately, it is of interest to incorporate all sample processing steps into such microsystems, to achieve what has come to be known as the miniaturized total analysis system (μTAS). A related development in recent years sees researchers exploring the use of micromachined structures for chemical synthesis of combinatorial libraries. The reduction of macroscopic industrial reactors to arrays of many parallel microreactors has also been proposed in the chemical engineering world, both for process optimization and actual production.

This course is an introductory overview of microsystems technologies for chemistry and life science applications. Emphasis will therefore be placed on describing basic micromachining technologies and how they are applied to engineering of chemical microsystems. Fundamental microfluidic concepts and the vocabulary used in this interdisciplinary will be presented. Examples of successfully implemented chip-based systems for chemical and biological research applications will be described, and trends in applications and microfluidic technologies discussed.

NEW TOPIC THIS YEAR: Production of MST-based microfluidic devices
As microsystems technologies mature and begin to emerge from the research lab, it is of increasing importance to consider the issues involved in the development of commercially viable products. This year's course will, for the first time, present the technologies available for the production of MST-based devices, and discuss the problems that typically need to be overcome to reach the marketplace.

Target Audience

This is an introductory course directed to scientists in the pharmaceutical and environmental industries and in clinical laboratories, at both the R & D management and laboratory levels. Participants will be provided with a foundation which may serve as an aid in the evaluation of microsystem technologies for their specific applications, or as a basis for further exploration of this fascinating research area. Given the wide scope of interest this technology has generated in chemical and biochemical fields, it is anticipated that course participants will come from a variety of different scientific backgrounds. The level of the course will be adjusted to allow for this diversity.

Course Instructors

Albert van den Berg
MESA+ Institute, University of Twente, Enschede, The Netherlands
Harald van Lintel
Department of Microtechnology, Federal Institute of Technology, Lausanne, Switzerland
Sabeth Verpoorte
Institute of Microtechnology, University of Neuchâtel, Neuchâtel, Switzerland
J. Malcolm Wilkinson
Technology For Industry Ltd., Cambridge, United Kingdom

SHORT COURSE

Topics to be covered

MICROFLUIDICS : BASICS

- scaling effects
- pumping mechanisms
- mixing
- micromachined pumps and valves
- sample filtration

MICROFLUIDICS : CHEMICAL/BIO-LOGICAL APPLICATIONS

- advantages of miniaturization for chemistry and biology
- evolution of the field
  - miniaturized total analysis systems (μTAS)
  - integrated fluidics
  - lab-on-a-chip (LOC) : μTAS / microreactors / microarrays
- drivers for LOC
- major applications
- sensor-based systems
- micro flow injection analysis (μFIA)
- electrokinetically driven systems

APPLICATION & MICROFLUIDIC TECHNOLOGY TRENDS :

- protein analysis with mass spectrometry
- increased integration / multiplexing
- microdevices for cell-based assays
- use of beads on chips
- chromatographic application trends
- miniaturized spectroscopy

MICROMACHINING :

- photolithography
- micromachining of silicon and glass
- etch techniques
- thin film deposition
- bonding techniques
- polymers

ENGINEERING CHEMICAL MICROSYSTEMS :

- design choices
- system simulation
- design for testing
- fabrication and packaging
- interfacing approaches
- development issues
- microsystem examples

PRODUCTION OF MICROFLUIDIC DEVICES :

- production technologies
- case studies of the commercialization of MST devices
- road maps for MST in (bio)medical applications

SHORT COURSE PROGRAM

Sunday, November 26

14.00 - 15.00 Registration & Welcome
(Coffee & juice will be served).

15.00 - 15.45 **Sabeth Verpoorte**
Advantages & Scope of Microtechnologies for Chemical/Life Science Applications

15.45 - 16.30 **Harald van Lintel**
Introduction to Micromachining

16.30 - 17.15 **Albert van den Berg**
Microfluidic Devices

17.15 - 18.00 **Malcolm Wilkinson**
Review of production Technologies for Microfluidic Devices

18.30 **Departure of Bus for Wine Tasting**

20.30 Return of Bus to Montreux

Monday, November 27

9.00 - 9.45 **Sabeth Verpoorte**
Electrokinetically Driven Microfluidic Systems

9.45 - 10:30 **Albert van den Berg**
Microfluidic Devices II

10.30 - 11.00 Coffee Break

11.00 - 11.45 **Harald van Lintel**
Design of Prototypes

11.45 - 12.30 **Albert van den Berg**
μTAS

12.30 - 14.00 Lunch Break on own

14.00 - 14.30 **Malcolm Wilkinson**
Commercial MST Devices: case Studies

14.30 - 15.00 **Harald van Lintel**
Microfluidics Research

15.00 - 15.15 Coffee Break

15.15 - 15.45 **Sabeth Verpoorte**
Application Trends

15.45 - 16.15 **Malcolm Wilkinson**
Road Maps for MST in (Bio)medical Applications

Short Course Social Event

On Sunday evening, fine wine and cheese will be served at the magnificent Château du Châtelard, overlooking Montreux and Lac Léman; this event is an opportunity for participants and instructors to continue the day's discussion in a more relaxed setting.

CONFERENCE PROGRAM

Tuesday, November 27

08.00 - 09.00 Registration

Chair: Philippe Renaud

09.00 - 09.05 **Philippe Renaud**, Program Chairman, Federal Institute of Technology, Lausanne, Switzerland
Opening & Welcome

09.05 - 09.50 **Jed Harrison**, University of Alberta, Canada
Can Proteomic Sample Preparation Provide a Killer Application for Microfluidics ?

09.50 - 10.20 **Gunther Fuhr** Humboldt University, Germany
Microsystems Technology and Cryo-Biology - A new field of Biotechnology ?

10.20 - 10.50 Coffee Break

Chair: Albert van den Berg

10.50 - 11.10 **Joël Rossier** DiagnoSwiss, Monthey, Switzerland
Disposable Electrochemical Chips for Immuno-assays and Nanospray-MS Analysis of Proteins

11.10 - 11.30 **Anders Palm** Gyros AB, Uppsala, Sweden
Integrating sample preparation for MALDI MS analysis on a disc

11.30 - 11.50 **Santeri Tuomikoski** Helsinki Univesyty of Technology
Preparation of porous n-type silicon sample plates for desorption/ ionization mass spectrometry

11.50 - 12.10 **Peter Spegel** Lund University, Sweden
New Approaches towards Size Selectivity in Capillary Electrophoresis for Trace Amount Protein Detection

12.10 - 12.20 Discussion

12.20 - 15.00 Lunch Break on own/Posters/Exhibition

Chair: Jed Harrison

15.00 - 15.30 **Andreas Manz** Imperial College, London, UK
Detection schemes for small volumes

15.30 - 15.50 **H. John Crabtree**
Microchip Injection and Separation Anomalies

15.50 - 16.10 **Andreas Gerlach** Greiner Bio-One GmbH,Germany
High Density Plastic Microfluidic Devices for CE-Separation and High Throughput Screening

16.10 - 16.30 **Sherri Biondi** Caliper Technologies Corporation, USA
High-Density Reagent Storage Arrays for High-Throughput Screening

16.30 – 16.50 **Holger Bartos** TSTEAG microParts GmbH, Germany
Novel Polymer based Biochips

16.50 - 17.10 Discussion

17.10 - 17.20 Session Break / Poster Session

17.20 - 17.30 **John Crabtree**, Micralyne, Canada
To be announced

17.30 - 17.40 **Malcolm Wilkinson**, Europractice, UK
To be announced

17.40 - 19.30 **Poster session – Exhibition**
Reception in the Exhibition Hall

20.00 **Banquet Dinner at the Palace Hotel**

Wednesday, November 28

Chair: Andreas Manz

09.00 - 09.30 **Wilhelm Ansorge**, EMBL, Heidelberg, Germany
Bridging Genomics and Proteomics : DNA and Protein Chips

09.30 - 09.50 **Urs Staufer** IMT, Neuchâtel, Switzerland
Single Molecule Detection by Contilever-based scanning near-field optical microscopy

09.50 - 10.10 **Staffan Nilsson** University of Lund, Sweden
Microfluidic handling in nanochemistry

10.10 - 10.30 **Jan Krüger** NMRC, Cork, Ireland
Development of a Microfluidic Device for Fluorescent Induced Cell sorting

10.30 - 11.00 Coffee Break / Exhibition

Chair: Günther Fuhr

11.10 - 11.30 **Dan Branton** Harvard University, USA
Probing bio-polymers with a nanopore

11.30 - 11.50 **Christian Schmidt** Cytion, Lausanne, Switzerland
Patch-clamp on a chip

11.50 - 12.10 **Boone Travis** Aclara, USA
Plastic Microfluidic Devices for Sub-Microliter Assays and Multiplexing

12.30 - 15.00 Posters/Exhibition/Lunch Break

Chair: Marc Madou

15.00 - 15.30 **Terence Coakley** School of Biosciences, Cardiff University, UK
Microparticle Motion and Suspending Phase Flows in Ultrasonic Standing Wave Mini-systems

15.30 - 15.50 **Kenji Yasuda** University of Tokyo , Japan
Non-destructive microscopic concentration, separation, analysis of biomaterials using acoustic radiation force

15.50 - 16.10 **Jeremy J. Hawkes** Cardiff University, UK
Positioning particles within liquids and gels using ultrasound force fields

16.10 - 16.30 **Jonathan West**, NMRC, Cork, Ireland
Annular magnetohydrodynamic actuation for cyclical chemical reactions

16.30 - 16.50 **Gian-Luca Lettieri** IMT, Neuchâtel, Switzerland
Planar microfluidic devices for affinity-based bioanalysis using beads

16.50 - 17.20 **Al Kolb** Technology Partnership, UK
Enhancing the Use of Microtechnologies with Automation

17.20 - 17.30 **Discussion**

17.30 - 19h30 **Poster session / Exhibition**

18h30 - 20h00 **Industry - Sponsored - Buffet**

Thursday, November 29

Chair: Sabeth Verpoorte

08.30 - 09.00 **Marc Madou** Nanogen, USA
MEMS and Biotechnology in the 21st Century

09.00 - 09.20 **Alexandra Fuchs** CEA, Grenoble, France
A hybrid plastic/silicon Lab-On-Chip for integrated PCR and hybridization

09.20 - 09.40 **Pascal Mayer** GenInEx, Geneva, Switzerland
DNA sequencing on self-forming micro-arrays: towards 1 milion bases/second/setup

09.40 - 10.00 **Helene Andersson** Royal Institute of Technology, Stockholm, Sweden
Self-Assembly and Immobilization of Micro- and Nano-Sized Particles for Biotechnical Applications

10.00 - 10.20 **Gert Desmet** Vrije Universiteit Brussel, Belgium
Enhancement of DNA Micro-array Analysis by Means of Shear-driven Flows.

10.20 - 10.50 *Coffee Break*

Chair: Staffan Nilsson

10.50 - 11.10 **Stephanie Wong** GlaxoSmithKline, UK
Why Microchemistry ?

11.10 - 11.30 **Shady Gawad** Swiss Federal Institute of Technology Lausanne Switzerland
On-chip flow cytometry and impedance spectroscopy

11.30 - 12.00 **Rudolf Rigler,** Karolinska Institutet, Stockholm, Sweden
Analysis and Handling of Single Molecules in Microstructures

12.00 - 12.05 **Philippe Renaud,** Program Chairman
Closure of the meeting

POSTER PRESENTATIONS

Atomic-force studies of biomolecules with lipid vesicle TAGs deposited onto thin film biochips
Yilmaz **Alguel**[2], Norbert Stich[1,2], Christian Mayer[1], and Thomas Schalkhammer[1,2]
[1] Kluyver Lab. for Biotechnology, TU-Delft, Julianalaan 67, 2628 BC Delft, The Netherlands, Tel.: 0031-15-278-9289, Fax.: 0031-15-278-2355
[2] Institut für Biochemie und Molekulare Zellbiologie, Universität Wien, Dr. Bohrgasse 9, A-1030 Vienna, Austria, Tel.: 0043-1-4277-52818, Fax.: 0043-1-4277-9528

Transport of sub-micron latex spheres by travelling-wave dielectrophoresis
Brian P. **Cahill**, Andreas C. Stemmer
Nanotechnology Group, Swiss Federal Institute of Technology Zurich

Microfluidics and microoptics in plastic
T. **Callenbach**, M. Gmuer and Ch. Becker
Weidmann Plastics Technology AG, Switzerland and USA

Structoplate: a newly developed 3d-microstructured surface in multiwell tissue culture plates
B. Saad[1,2,3], T. **Callenbach**[4], K. Brander[5], M. Welti[2], G.K. Uhlschmid[2] and U.W. Suter[1]
[1] Department of Materials, Institute of Polymers, ETH, CH-8092 Zurich,
[2] Research Division, Department of Surgery, University Hospital, CH-8091 Zurich,
[3] Arab American University Jenin-PA,
[4] Weidmann Plastics Technology AG, CH-8640 Rapperswil,
[5] Integra Biosciences Holding AG CH-6274 Eschenbach

Micro fabrication for planar mikrofluidic devices
Jie-Wei **Chen**
Leister Process Technologies, Sarnen, Switzerland

DNA Markers Separation on Micro-channel Electrophoresis Chip using Laser-Induced- Fluorescence Detection
Jifeng **Chen**, Qinghui Jin, Jianlong Zhao, Yuansen Xu
Shanghai Institute of Microsystem and Information Technology, Chinese Academy of Sciences, Shanghai, PR China

Synthesis of nanostructured ceramic powders using a novel and versatile chemical method
N. N. **Ghosh**
Chemistry Group, Birla Institute of Technology and Science - Pilani, Rajasthan - 333031, India

Biosystem for epithelial cell culture and electrical characterisation.
S.**Hediger**[1], A.Sayah[1], J.D. Horisberger[2], and M.A.M. Gijs[1]
[1]Institute of Microsystems, Swiss Federal Institute of Technology Lausanne, CH-1015 Lausanne EPFL, Switzerland
[2]Institute of Pharmacology and Toxicology, University of Lausanne, CH-1005 Lausanne UNIL, Switzerland

POSTER PRESENTATIONS

Coherent Porous Silicon (Cps) As A Basis For Micro Heatpipes And Airborne Bio-Organism Selectors
H. Thurman **Henderson** And Frank M. Gerner
University Of Cincinnati, Center For Microelectronic Sensors And Mems

Approaches to Fabricate Complex Microfluidic Channelsystems for the Molecularbiology
Steffen **Howitz**[1], Thomas Gehring[1], Lars Rebenklau[2], Andreas Richter[2]
[1] GeSiM mbH, Germany
[2] Dresden University of Technology, Germany

On-Channel Sample Stacking with Twin-T Injector on Microchip Electrophoresis
Qinghui **Jin**, Jifeng Chen, Tie Li, Ji Wang, Jianlong Zhao, Yuansen Xu
Shanghai Institute of Metallurgy, Chinese Academy of Sciences, Shanghai P.R.China

Integrated Nanoporous Membranes in Polymer Channels
Stefan **Metz** and Philipe Renaud
Institute of Microsystems, Swiss Federal Institute of Technology Lausanne, CH-1015 Lausanne EPFL, Switzerland

Kinetics of DNA Hybridization in Flow-Through Nano-Channels
K. **Pappaert**[1], J. Vanderhoeven[1], P. Van Hummelen[2], G. V. Baron[1] and G. Desmet[1]
[1] Department of Chemical Engineering, Vrije Universiteit Brussel, Belgium
[2] MicroArrayFacility Lab, Flemish Institute for Biotechnology (VIB), Belgium

Fast Chiral On-Chip Separations with Amperometric Detection
Maria A. **Schwarz** and Peter C. Hauser
The University of Basel, Department of Chemistry, Switzerland

Characterisation of MEMS mechanical properties using nanoscale techniques
N. **Randall** and R. Soden
CSEM Instruments S.A., Neuchâtel, Switzerland

Electrochromatography chip with low dead-volume lateral capillary connections
D. **Solignac**[1], L. Szekely[2], A. Sayah[1], S. Constantin[2], R. Freitag[2], and M.A.M. Gijs[1]
[1] Institute of Microsystems, Swiss Federal Institute of Technology Lausanne, CH-1015 Lausanne EPFL, Switzerland
[2] Centre of Biotechnology, Swiss Federal Institute of Technology Lausanne, CH-1015 Lausanne EPFL, Switzerland

POSTER PRESENTATIONS

A novel process for high speed, multi-column separations at the nanoliter scale
Ebru **Togan-Tekin**, Helene Dérand, Ulrike Selditz, Gunnar Ekstrand, Susanne Wallenborg, Anders Palm, Magnus Gustafsson, Gunnar Thorsen, Per Andersson
Gyros AB, Uppsala Science Park, SE-751 83 Uppsala, Sweden
www.gyosmicro.com

Simulation of transdermal-delivery drug models: 4-alkylanilines
Francisco **Torrens**
Departament de Química Física, Facultat de Química, Universitat de València, Spain.

Adhesive bonding of channel structures using a patternable UV-sensitive glue
Heiko **van der Linden**, Wouter Olthuis, Piet Bergveld
e-mail: h.j.vanderlinden@el.utwente.nl
MESA+ Research Institute, Twente University
Drienerlolaan 5, P.O. Box 217, 7500 AE
Enschede, The Netherlands

Time-resolved electrochemiluminoimmunoassay of hCRP at oxide-coated p-type silicon electrodes
Piia **Vainio**[1],Timo Ala-Kleme[1], Leif Väre[1] , Markus Håkansson[2], Philip Canty[2], Jarkko Eskola[3], Sami Franssila[4] and Sakari Kulmala[2*]
[1]Laboratory of Analytical Chemistry, University of Turku, FIN-20014 Turku, Finland
[2]Laboratory of Inorganic and Analytical Chemistry, Helsinki University of Technology.
[3]Labmaster Oy, P.O. Box 71, FIN-20521, Turku
[4]Microelectronics Centre, Helsinki University of Technology, Finland

Ultrasonic trapping for improved concentration limit of detection in capillary electrophoresis
M. **Wiklund**[1], P. Spégel[2], S. Nilsson[2] and H. M. Hertz[1]
[1]Biomedical and X-Ray Physics, Royal Institute of Technology,/SCFAB, SE-106 91 Stockholm, Sweden
[2]Technical Analytical Chemistry, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden

EXHIBITION

What's on Display

Leaders in industry and academia will be coming together in a state-of-the art exhibition that will take place in the hall adjacent to the conference room. Research institutions and universities will be presenting their projects in the field, while industrial companies will be showing their products, such as fluid micro-dispensing devices, sensors, biosensors and miniaturized robots with the capacity to move single cells. This unique event will be devoted exclusively to the present state and future of the field, giving exposure to the latest products and approaches, as well as to projects currently under development.

The exhibition will take place in Léman B and C of the Montreux Palace's Petit Palais.

EXHIBITORS

13 **AMT Application Center for Microtechnology**, Jena, Germany
14 **BTI BIOTECH international,** Brussels, Belgium
12 **ROYAL SOCIETY OF CHEMISTRY,** Cambridge, UK
6 **Nanogen Europe**, Helmond, The Netherlands
4 **Evotec OAI AG**, Hamburg, Germany
2 **ISC International Scientific Communications**, UK
9 **Europractice**, Wilburton, UK
7 **IMT Intitute of Microtechnology**, Neuchâtel, Switzerland
3 **Jenway Limited**, Dunmow, UK
1 **Micralyne**, Edmonton, Canada
10 **MESA+ Institute**, Enschede, The Netherlands
10 **Micronit Microfluidics**, Enschede, The Netherlands
3 **Mildendo GmbH**, Jena, Germany
5 **G.I.T. VERLAG PUBLISHING LTD**, Darmstadt, Germany
11 **Swiss Federal Institute of Technology**, Lausanne, Switzerland
8 **Parabol Technologies,** Lausanne, Switzerland

Micro surgery on deep-frozen individual cells

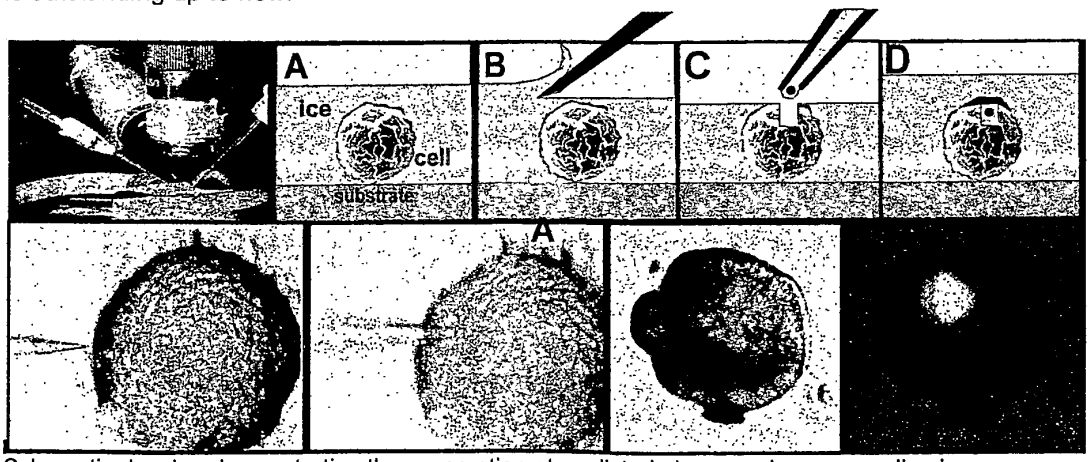
Günter R. Fuhr
Fraunhofer Institute for Biomedical Engineering, Ensheimer Strasse 48, 66386 St. Ingbert, Germany

The cryo-conservation of cells is a well established technique applied since decades in medicine, biology, pharmacology and since several years more and more also in biotechnology. Most common is the deposition of cell suspensions in ml-plastic vials. Less investigated is the cryo-conservation of adherently growing cells, especially in small volumes (µl and less). However, the developing molecular and cellular biotechnology requires such procedures to store and transfer living cell biosensors, cell layers or tissue-like substrates. Additionally, there is an increasing need in highly accurate cell manipulation techniques to remove, to change or to transfer biological or artificial material from or into individual cells. At physiological temperatures cell manipulation is strongly time limited and cells are very sensitive.

In a two year research program we have tested the possibility to develop a deep temperature cell manipulation technique. In particular, the following steps should be realized and tested:

1. Deposition of single cells in micro wells
2. Microscopic imaging of single cells at sub-zero temperatures (between -10 °C to -150 °C)
3. Preparation of the cell surface
4. Partial opening of the cell
5. Remove of material
6. Insertion of artificial material
7. Closing the cell wounding
8. Covering the cell with physiological solution
9. Thawing the cell
10. Proof of integrity
11. Proof of cell vitality

As shown in the Figure, points 1 to 10 could be successfully realized. The proof of cell vitality is outstanding up to now.



Schematic drawing demonstrating the preparation steps listed above and corresponding images below. Shown is an egg cell of *Ophryotrocha puerilis*, diameter around 100 µm. A) Preparation of the cell surface, B) Opening of the cell envelope under nitrogen atmosphere, C) Insertion of a fluorescent nanobead, D) Closing the cell wounding and view after defrosting in suspension.

Summarizing, it could be demonstrated that deep-temperature micro surgery at individual cells could be a new way for biotechnology and related fields to manipulate on the single cell level with highest precision and low time limitation. During the talk the strategy, technical developments and results are presented.

High-Speed, Single Molecule Gene Probing using Self Assembled and Solid State Nanopores. Daniel Branton and Jene Golovchenko, Harvard University, Cambridge, MA 02138, USA

We are developing nanopore technology for probing genes and eventually sequencing DNA molecules. Our discovery[1] that a voltage bias can drive single-stranded polynucleotides of great length through a 1-2 nanometer transmembrane channel, or nanopore, has led to the demonstration that the electrical signals obtained from such a pore can rapidly characterize biological polymers[2,3,4] (Figure 1).

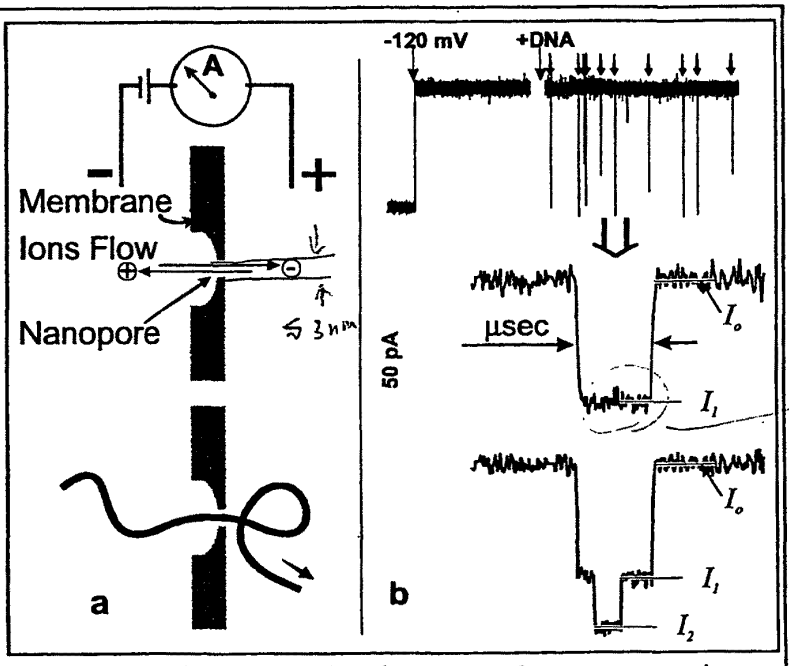


Figure 1. Principles and components of a nanopore device for characterizing the length, and other features along the length, of a DNA molecule. (*a*) A channel or nanopore in an insulating membrane separates two ionic solution-filled compartments. Electrodes are used to apply a voltage bias, labeled "–" and "+", across the membrane. (*top*) In response to this bias, ions flow through the open nanopore. A picoameter measures ion flow. (*bottom*) When DNA molecules are added to the "-" compartment, these negatively charged molecules are drawn, one at a time, into and through the channel. Because the translocating DNA partially obstructs or blocks the nanopore, it alters the pore's ionic conductivity. (*b, Top and middle*) Recording from an experiment using a lipid bilayer membrane and *S. aureus* α-hemolysin as the nanopore. The voltage applied across the bilayer (-120 mV) produces a current of ions that pass through the nanopore. After adding DNA, transient reductions of the current (from I_o to I_1) are evident (arrows) as DNA molecules are drawn through the channel[1]. Because the nanopore in the α-hemolysin channel is wide enough to admit only a single strand of DNA, the DNA nucleotides translocate across the membrane in strictly single-file order. Thus, the time it takes for the DNA strand to be drawn through the channel (*enlarged view in middle pannel*) is a measure of the DNA molecule length. (*b, bottom*) Cartoon showing how secondary structure or bulky labels attached along the length of the DNA would further obstruct the nanopore, thus causing additional current reductions (from I_1 to I_2) as the structured or labeled region of the DNA translocates through the nanopore.

Among the unique features of this nanoscale device, four demonstrated capabilities that make it possible to probe DNA stand out:

1. The method directly converts characteristic features of the translocating polymer into an electrical signal at rates exceeding 100 bases per millisecond. Transduction and recognition occur in real time, on a molecule-by-molecule basis.
2. A nanopore is a single molecule detector, but it functions as a high throughput device. Thousands of different molecules or thousands of identical molecules can be probed in a few minutes.
3. Channel blockage is sensitive to the local cross-sectional area of the molecule. When polymers whose cross-sectional area is increased by secondary structure translocate through the pore, more of the current is blocked (less current flows) than when a strand lacking such secondary structure translocates through the pore.
4. Long lengths of DNA can be probed. Although practical considerations may limit the length of DNA that is detected as it translocates through a nanopore, we are not aware of any theoretical limits.

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1. Kasianowicz, J.J., E. Brandin, D. Branton, and D.W. Deamer. 1996. Characterization of individual polynucleotide molecules using a membrane channel. *Proc. Natl. Acad. Sci. USA* 93: 13770-13773.
2. Akeson, M., D. Branton, J.J. Kasianowicz, E. Brandin, and D.W. Deamer. 1999. Microsecond time-scale discrimination among polycytidylic acid, polyadenylic acid, and polyuridylic acid as homopolymers or as segments within single RNA molecules. *Biophys. J.* 77: 3227-3233.
3. Meller, A., L. Nivon, E. Brandin, J. Golovchenko, and D. Branton. 2000. Rapid nanopore discrimination between single polynucleotide molecules. *Proc. Natl. Acad. Sci. USA* **97**: 1079-1084.
4. Meller, A., L. Nivon, and D. Branton. 2001. Voltage-driven DNA translocations through a nanopore. *Phys. Rev. Lett.* **86**:3435-3438.

Non-destructive microscopic concentration, separation, analysis of biomaterials using acoustic radiation force

Kenji Yasuda

Department of Life Sciences, Graduate School of Arts and Sciences, University of Tokyo

A method for non-contact handling of biological materials such as erythrocytes could be incorporated in a fully automated analysis system providing contamination-free, real-time measurement. One non-contact force having several advantages for handling biomaterials is acoustic radiation force. Benefits of the use of acoustic radiation force for handling biomaterials are (1) simple and compact design without moving parts, (2) suitability for continuous concentration, separation and mixing, and (3) ready use in microchamber allowing contamination-free handling. Since this can be an advantage in biological applications, we pursue such handling techniques using ultrasound.

Mixing, Concentration and fractionation of biomaterials [1-4]: The ultrasonic standing plane wave (input 120V_{pp} at 500 kHz) was applied to concentration of biomaterials like DNA, and red blood cells [1,2]. After the ultrasonic irradiation started, 3kbp DNA clusters in ethanol solution started moving toward the pressure node of the ultrasonic stationary standing wave and then gathered to form a larger cluster. Red blood cells also gathered to the pressure node by the acoustic radiation force within 10 sec. Under these conditions, the damage caused by ultrasound has also studied. While DNA fragmentation was checked by electrophoresis after 10 min ultrasound irradiation, no significant change in nucleotize size was observed. The extent of possible release inflicted on erythrocytes by acoustic radiation force when the cells are concentrated by a 500 kHz ultrasonic standing wave at the pressure node was measured, and no significant release of erythrocyte components such as potasium ions was detected, even after 15 min irradiation. The results indicate that in the absence of cavitation even small ions like potassium are not released as a result of ultrasound irradiation on cell membranes, and they demonstrate the potential use of acoustic radiation force for concentrating living cells in biomedical applications. The concentrating technique was applied to the fractionation of polystyrene spheres 10 μm in diameter by using a capillary tube [3]. More than 90 % of the particles in a laminar flow were successfully collected. For mixing, samples such as erythrocytes and fluorescent dye were introduced into the chamber from the inlet which arranged at the side wall of the chamber and the laminar flow of two different kinds of solutions keeping their boundaries has observed. When 3.5 MHz ultrasound irradiation into the chamber started, the boundaries of two sample's flow was broken and erythrocytes spreaded and mixed into all the span of the chamber. The possible damage caused by 3.5 MHz ultrasound during mixing process was also measured, and no significant release of erythrocyte's component was detected even without degas process, which was pre-processed for preventing cavitation generation. The results suggested the potential use of acoustic radiation force for non-contact, non-destructive and time resolved handling method for micro-chamber as the sample preparation process [4].

Superposition method for improving concentrating efficiency [5]: A method for improving the concentration efficiency of particles keeping halfwidth of standing wave has been investigated. The efficiency of concentration of blood cells by the superposition method was theoretically improved 20 % better than that using sine wave and was experimentally improved 5 %. Though the experimental result was insufficient to realize the theoretical estimation for lack of complete waveform of ultrasound, the potential of the use of the superposition method was demonstrated. We also applied this method for shifting pressure nodes from one side to the another side wall. Using this technique the efficathy

Separation of different materials exploiting the competition between acoustic radi ation force and electrostatic force [6, 7, 8]: The separation of particles in liquid by competition between acoustic radiation force and electrostatic force was also tested. The displacement of particles from the pressure node of an ultrasonic standing wave is expected to vary according to the effective charge, radius and stiffness of the particles. By application of this technique, a mixture of polystyrene spheres with two different radii was successfully separated according to their radii.

References:

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[8] K. Yasuda, Jpn. J. Appl. Phys., **38**, pp.3316-3319 (1999).

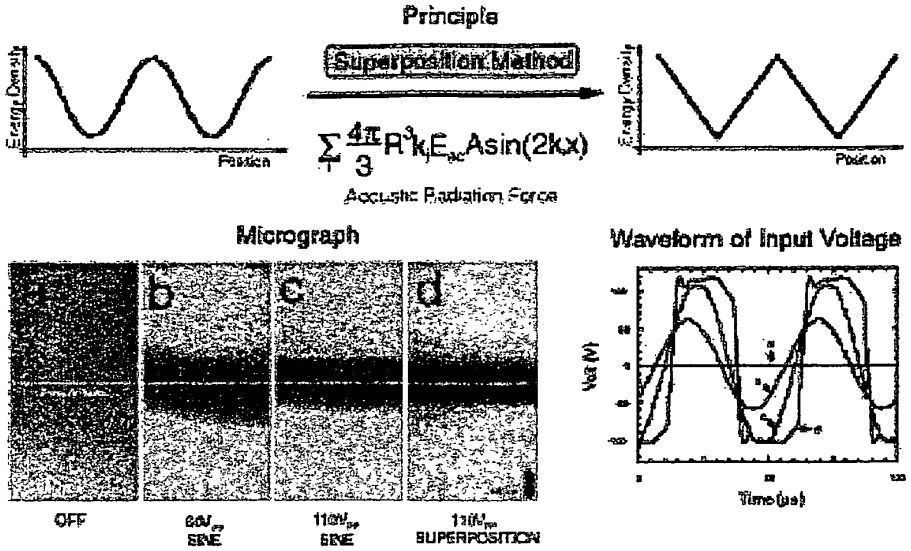

Fig.1 One example of acoustic radiation force for handling of microparticles; superposition method for improving concentration efficiency of blood cells; (a) before ultrasound irradiation, (b),(c) ultrasound sine wave, (d) ultrasound superimposed wave. Erythrocytes gathered on the pressure nodes in the standing wave.

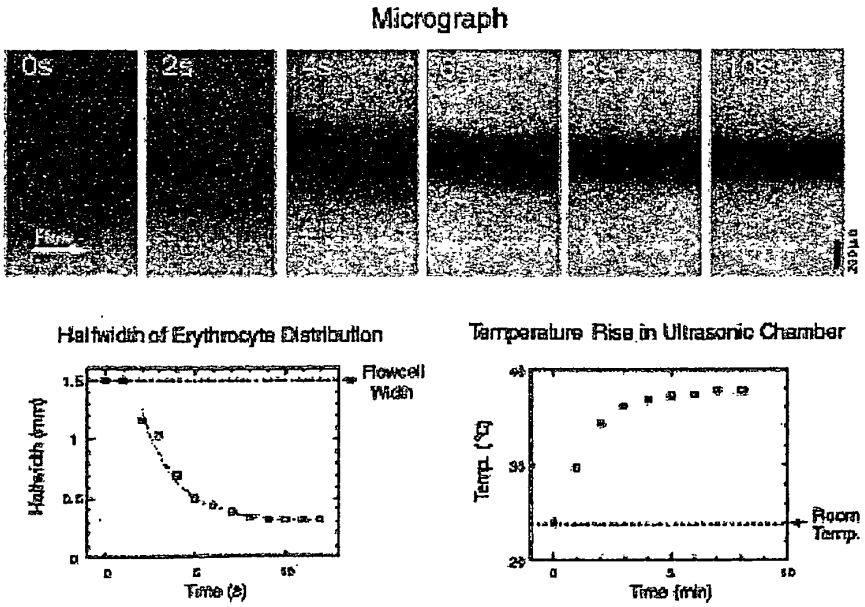

Fig.2 Time course of blood concentration using superposition method. Erythrocytes are concentrated at the pressure node within 10s.

SEPTEMBER 2001

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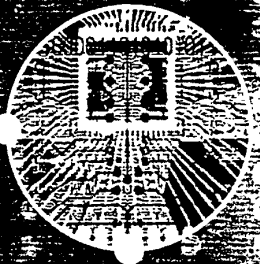
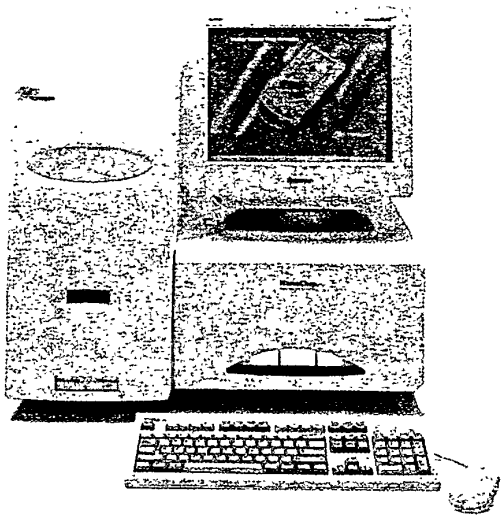


RSC

Nanogen

NanoChip™

Molecular Biology Workstation



NanoChip™ Reader NCR-1000

NanoChip™ Reader (Array Processor and Scanner)

Physical

Height	0.61 m	Depth	0.69 m
Width	0.70 m	Weight	66.2 kg

Electrical Supply

Line Voltage Power	100–120 VAC / 220–240 VAC; 10/6 Amps
Line Frequency	50/60 Hz
Fluctuation	Main supply voltage not to exceed ±10% of nominal supply
Class 1 (grounded)	

Capacity

Cartridge Capacity	1 NanoChip™ cartridge

Assay Conditions

Hybridization	Electronically-accelerated
Stringency	Thermal and/or chemical

Sample Format

Sample carrier	NanoChip™ cartridge
Sample attached to array	Biotinylated 10–400 bp nucleic acid fragments
Sample for hybridization	10–400 bp nucleic acid fragments (<250 optimal)

Laser Information

Laser I (red laser):	Excitation Wavelength 635 nm
Laser II (green laser):	Excitation Wavelength 532 nm
Class I Laser Product	

NanoChip™ Reader (continued)

Detection Specifications

Detector	Photomultiplier Tube
Emission Wavelength I:	660–720 nm
Emission Wavelength II:	550–600 nm

Environmental Conditions

Temperature	18–30°C
Humidity	40-75% noncondensing
Pollution degree	2
Installation category	II
Altitude	up to 2000 m

NanoChip™ Loader (Electronic Arrayer)

Physical

Height	0.30 m	Depth	0.57 m
Width	0.69 m	Weight	51.0 kg

Electrical Supply

Line Voltage Power	100–120 VAC / 220–240 VAC; 6/4 Amps
Line Frequency	50/60 Hz
Fluctuation	Main supply voltage not to exceed ±10% of nominal supply
Class 1 (grounded)	

Capacity

Cartridge Capacity	1–4 NanoChip™ cartridges

Assay Conditions

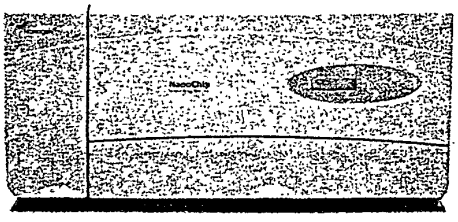
Array addressing method	Electronically-driven
Hybridization	Electronically-accelerated
Stringency	Chemical

Sample Format

Sample carrier	96-well or 384-well microtiter® plate to NanoChip™ cartridge
Sample attached to array	Biotinylated 10–400 bp nucleic acid fragments
Sample for hybridization	10–400 bp nucleic acid fragments (<250 optimal)

Environmental Conditions

Temperature	18–30°C
Humidity	40–75% noncondensing
Pollution degree	2
Installation category	II
Altitude	up to 2000 m



NanoChip™ Loader NCL-1000

electricity the future of genetic testing

Nanogen Europe B.V. - Steenovenweg 3 - 5708 HN - Helmond, Netherlands

NanoChip™ Cartridge (Microelectronic Array)

Chip Size
0.7 cm square

Array Dimensions
2 mm square

Array Site Size
80 microns

Distance between Site Centers
200 microns

Number of Test Sites
100

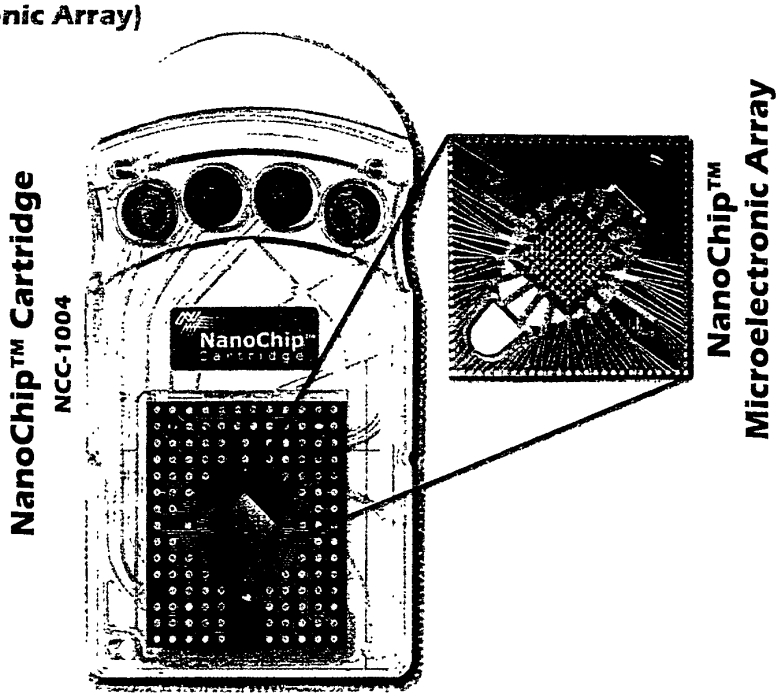
Permeation Layer
Thin hydrogel layer incorporating streptavidin

Binding Chemistry for Customizing Arrays
Electronically-driven streptavidin/biotin binding

Maximum Loading Density
Approximately 10^9 fragments per site

Minimum Sample Volume
40 µL

Storage Conditions
2–8°C



Data Analysis Computer Requirements

PC
IBM®-compatible Pentium® class

RAM
64 MB minimum

Browser Software Requirement (one of the following):
Microsoft® Internet Explorer 4.01 or higher
Netscape® Communicator 4.74 or higher (excluding version 6.0)

Free Hard-Drive Disk Space
10 MB minimum

Operating System
Microsoft® Windows® 9x/NT

Other Requirements
Ethernet port
CD-ROM drive
PC-compatible printer

Nanogen-Supported Assays

SNP Analysis: See Applications Guide

STR Analysis: See Applications Guide

Experimental Methodologies

"Pathogen analysis and genetic predisposition testing using microelectronic arrays and isothermal amplification," Edman, et al., *Journal of Investigative Medicine*, Vol 48, No 2: 93–101, March 2000.

"Anchored multiplex amplification on a microelectronic chip array," Westin, et al., *Nature Biotechnology*, Vol 18: 400–408, February 2000.

"Rapid high fidelity analysis of simple sequence repeats on an electronically active DNA microchip," Radtkey, et al., *Nucleic Acids Research*, January 2000.

"Active microelectronic chip devices which utilize controlled electrophoretic fields for multiplex DNA hybridization and other genomic applications," Heller, et al., *Electrophoresis 2000*, Vol 21: 157–164.

"Preparation and hybridization analysis of DNA/RNA from *E. coli* on microfabricated bioelectronic chips," Cheng, et al., *Nature Biotechnology*, Vol 16, No 6: 542–546, June 1998.

"Isolation of cultured cervical carcinoma cells mixed with peripheral blood cells on a bioelectronic chip," Cheng, et al., *Analytical Chemistry*, Vol 70, No 7: 2321–2326, 1998.

"Rapid determination of single base mismatch mutations in DNA hybrids by direct electric field control," Sosnowski, et al., *Proc. Natl. Acad. Sci. USA*, Vol 94: 1119–1123, February 1997.

"Electric field directed nucleic acid hybridization on microchips," Edman, et al., *Nucleic Acids Research*, Vol 25, No 24: 4907–4914, November 1997.

"An active microelectronics device for multiplex DNA analysis," M. Heller, *IEEE Engineering in Medicine and Biology*, 100–104, March/April 1996.

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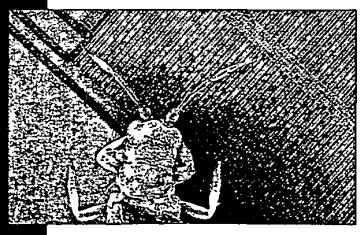
BOSCH

Acceleration
Movement
Tilt
Angular Rate
Angular Acceleration

Micromachined Sensors



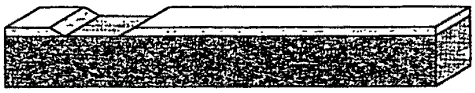
EUROPRACTICE
MICROSYSTEMS

BOSCH Surface Micromachining

In sensor technology we currently observe the same trend as in electronic circuits some decades ago: the market demands smaller devices with higher functionality and performance. And again it is silicon technology that helps to meet these requirements and at the same time reduces the costs for fabrication.

Based on well-established IC processes, silicon micromachining employs the same deposition and patterning techniques to form the desired electronic circuit on top of a silicon chip. But as an extension to common IC processing, in micromachining technology special structures are partially released thus providing a movable mass that reacts on mechanical forces by a microscopic deflection.

At Bosch we have developed a new surface micromachining process which is particularly suited for the manufacturing of high-performance inertial sensors. Using this process millions of sensors are already being produced each year.



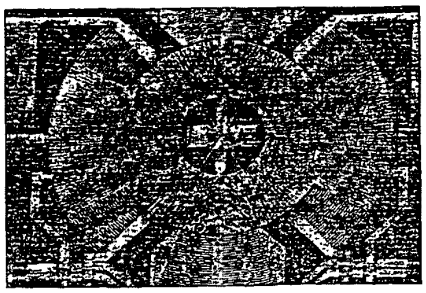
Deposition and structuring of sacrificial layer (yellow)

Deposition of polysilicon (blue)

Structuring of polysilicon

Removal of sacrificial layer

BOSCH process flow

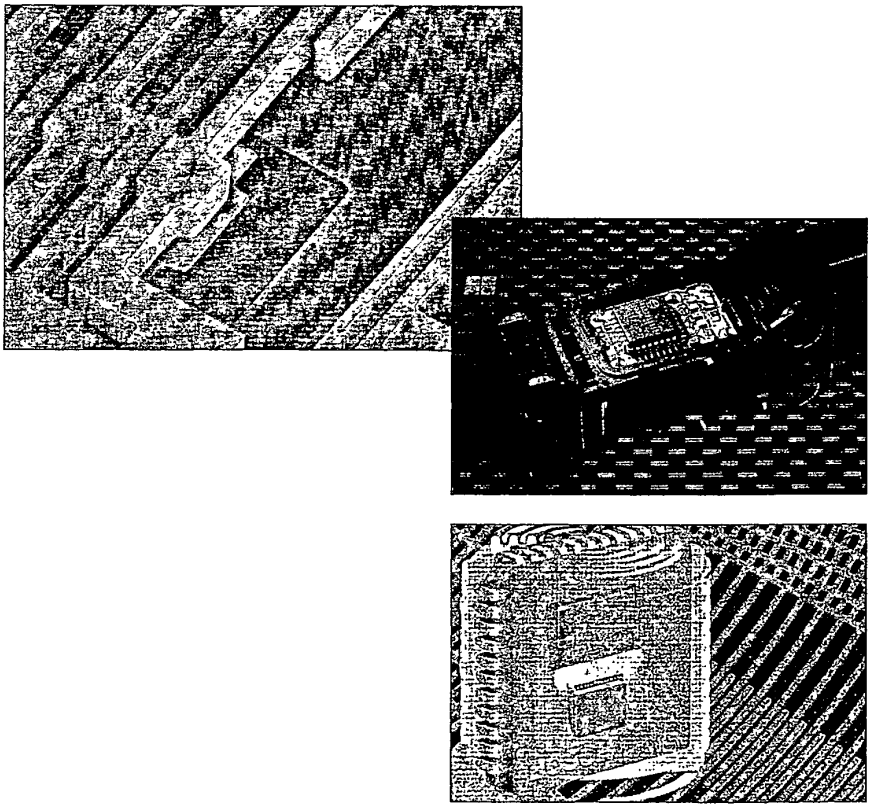


Product Example: Accelerometers

Accelerometers can be applied in a large number of products. Depending on the design they can be used for the measurement of acceleration and deceleration, shock, tilt, movement or vibration. Examples include the use in highly demanding automotive applications such as airbag control units, antilock-breaking systems and vehicle dynamics control systems.

For these and other applications Bosch has developed a family of accelerometers using its advanced silicon surface micromachining process. Available measurement ranges are starting from 1 g_N up to 250 g_N. The sensors use a capacitive detection scheme and can measure static as well as dynamic accelerations with high sensitivity.

A second product family based on the described technology is a new generation of gyroscopes. Benefits of these new devices are the clearly reduced size as well as the standard SMD pachage.

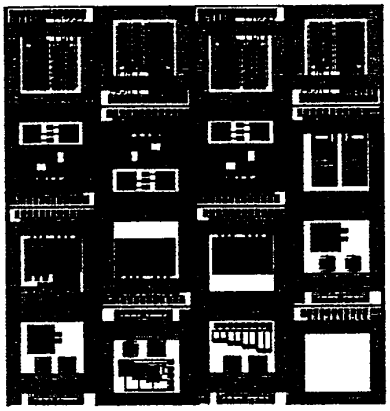


Services:

Bosch offers its experience and expertise in the area of micromachining and microsensors – comprising product development, application engineering and manufacturing – to customers.

In the framework of a professional foundry service for micromachined sensor elements, customers from research institutes as well as from the industry have access to the well developed fabrication facilities of Bosch in order to develop their own MEMS products.

To facilitate research, development and prototyping of customer specific micromachined parts at reasonable costs, Bosch is offering a multi-project-wafer (MPW) service. Several users share mask-costs for a particular fabrication run. These MPW runs are scheduled regularly, several times each year. The Bosch foundry service is supported by EUROPRACTICE.



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Fraunhofer Institut
Angewandte Optik
und Feinmechanik

Miniaturized Biochip

Aim

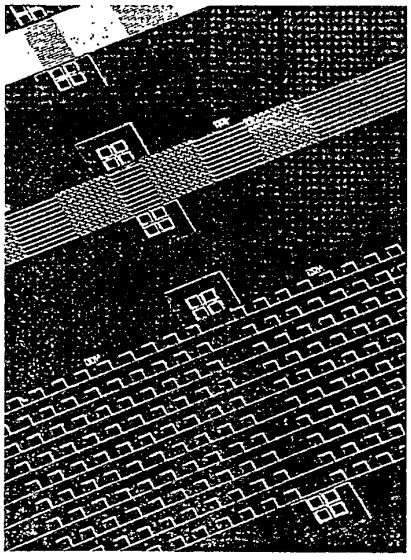
Highly sensitive molecule detection in two-dimensional arrays with minimum of sample volume

Biochip design

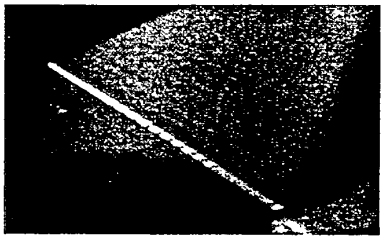
- Hydrophilic / hydrophobic patterned analyte areas for high density arrays for fluorescence analysis
- Pattern of thin Teflon AF ® layers onto different substrates (e.g. glasses, silicon, polymers)
- Optical excitation with waveguides arranged below the sample array

Applications

- Pharmaceutical drug discovery
  High Throughput Screening (HTS)
- Life sciences, diagnostics



Miniaturized, patterned, integrated optical Biochip for fluorescence analysis



Fluorescence excitation of a chip with adsorbed dye at 500nm wavelength

Specifications

- Limit of sensitivity:
  c ~ 10^{-8} Mol / l concentration
  Rhodamine 6G in water
  ρ ~ 1 molecule / μm^2
  area density
- Sizes of sample areas and waveguide widths down to a few micrometers
- Fluorescence excitation in the visible and NIR spectral range
- Low waveguide losses and material luminescence

Advantages

- Highly sensitive parallel analysis with minimum amount of analytes is possible: excitation volumes of 10^{-6}...$<10^{-15}$ liters
- Minimum amount of chemicals
- Optimum wetting behaviour
- Minimum adsorption outside the sample areas
- Spatial separation between excitation and detection channel
- Only molecules in the vicinity of the surface will be excited
- Combination with time resolved measurement techniques possible

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May 2000

Fraunhofer Institut Angewandte Optik und Feinmechanik

GRAFFINITY

Planar Biosensor - Array

Aim

Detection of molecules or molecular interaction at surfaces

Method

The principle of the sensor is based on the effect of surface plasmon resonance. Molecular interaction is detected optically by evaluating spectral transmission. Integrated optical waveguides are used for light excitation of sensor areas and detection.

Specification

- Detection limit:
  Sucrose in aqueous solution
  $\Delta c > 7$ mg/ml
  refractive index $\Delta n > 1 \times 10^{-3}$
- Lateral waveguide dimensions
  height < 500 µm
  width > 20 µm
- Spectral range 400 ... 1000 nm

Advantages

- Label free method that determines refractive index changes
- Sensor manufactured by established planar technologies
- One dimensional arrays enable parallel measurements
- Expandable to a 2D-sensor array for HTS-applications
- A high level of integration can be realized
- Adaptation to existing formats (up to 1536- well plates or higher)
- Sensors can be used in reflection or transmission mode

Applications

- Pharmaceutical drug discovery
  High Throughput Screening (HTS)
- Diagnostics
- Biochemical Application is offered by Graffinity Pharmaceutical Design GmbH, Heidelberg (exclusive exploitation)

Graffinity Pharmaceutical Design GmbH

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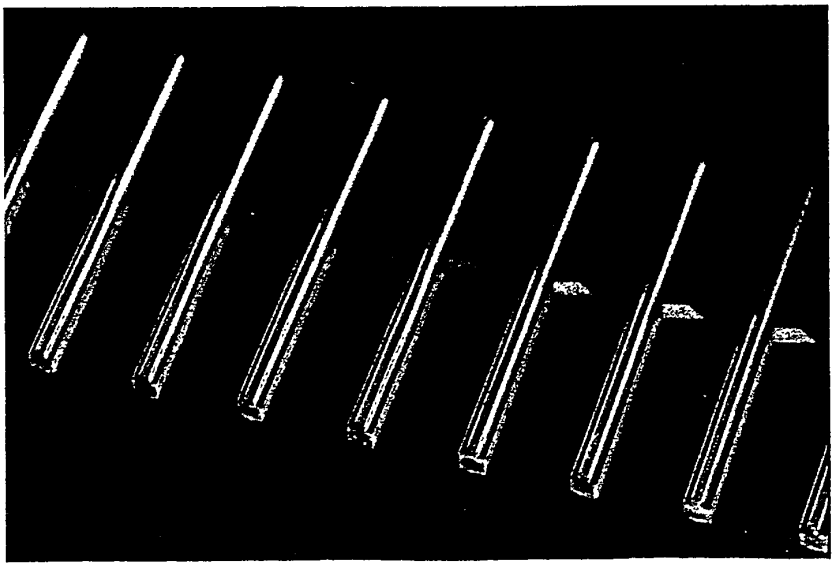
May 2000



Planar SPR-Biosensor-Array based on integrated optical waveguides

DETECTION TECHNOLOGY MILLIPORE

FIDA

Molecular Brightness

A Unique Sensor for a Variety of Molecular Interactions

evotec OAI

FIDA is a powerful technique for probing molecular brightness. Using FIDA, multiple fluorescent species in a homogenous assay format can be resolved through their specific molecular brightness[2]. The confocal nature of this technique enables single molecule sensitivity. The specific molecular brightness of a fluorescent species represents a very sensitive parameter, which can be perturbed by several microenvironmental effects.

FIDA is a novel technology for characterising biological interactions. Biomolecular binding reactions, intra- and intermolecular conformational changes, and changes of the macro- and microenvironment can be observed on a molecular basis with unrivalled accuracy.

FIDA is the only technology available which enables the study of binding of labelled ligands to targets expressing multiple binding sites such as vesicles, nanoparticles, protein aggregates etc. in homogenous assay formats.

KEY APPLICATIONS

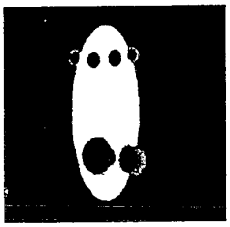
- bead based assays: nanoparticle immunoassays (NPIA), nucleic acid hybridisation onto capture beads
- vesicular assays: *In-situ* receptor-ligand interaction on membrane derived vesicles, tool box assay system for membrane integrated receptors (VLIPs: virus like particles)
- rare particle detection: incorporation of a beam-scanner enables fast and efficient detection of rare events down to femtomolar concentrations, e.g. protein aggregation processes may be monitored

KEY FEATURES

- background signal filter: enables artefact free analysis even in the presence of fluorescent impurities or high background signal
- molecular brightness: sensitive fundamental parameter that gives access to nearly all biomolecular interactions (generic).

TECHNOLOGY PRINCIPLE

The distribution of photon count numbers is used to differentiate certain molecular species through their specific molecular brightness. Concentrations of each species in a heterogeneous sample can be determined with superior accuracy.



low specific brightness (dim)

high specific brightness (bright)

FIG. 1 Principle of FIDA

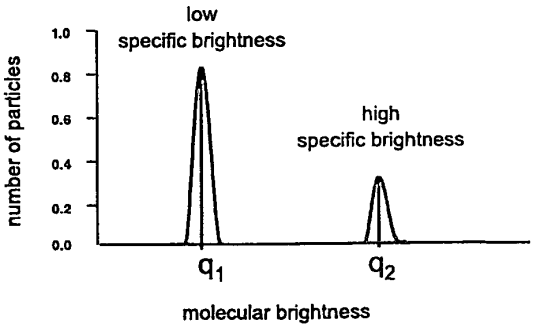


FIG. 2 Typical multi-component data distribution obtained using FIDA

READ OUT

Single molecule resolution of multiple molecular species:

- specific molecular brightness q
- absolute molecular concentration

Molecular brightness (q) may be perturbed by :

- fluorescence quenching / enhancement of the fluorescence tag
- spectral shift of the fluorophore
- quantum yield / fluorescence energy transfer
- binding to molecules with multiple binding sites

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evotec OAI

APPLICATION

For the purification of antibodies by affinity chromatography, protein A is used as an antibody-binding ligand. This method is accompanied by the risk of contamination with bacterial protein A. Since contamination of protein A may cause severe health problems in humans, highly sensitive, quantitative detection of protein A is essential for quality control in manufacturing of therapeutical antibodies and proteins.

Evotec OAI´s protein A assay is based on a sandwich immunoassay principle (FIG. 3) using streptavidin coated nanoparticles and two types of anti-protein A antibodies[1]. The biotinylated antibodies are used for capture of the analyte (protein A) and the fluorescently-labelled antibodies for detection. In the presence of protein A, sandwich complexes consisting of analyte, capture and detection antibodies are formed on the nanoparticle surfaces. To determine the protein A concentration, quantitative detection of these complexes is performed by FIDA[2].

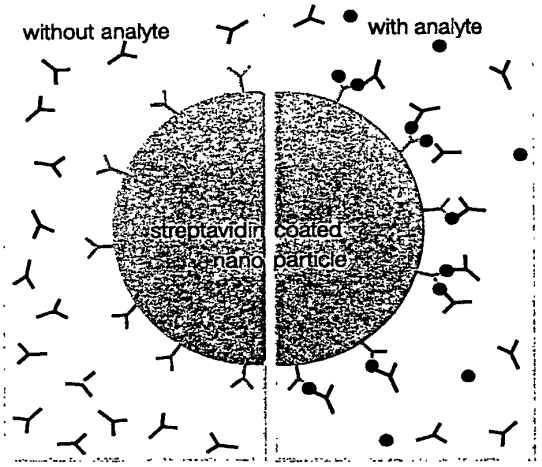

FIG. 3 Principle of Evotec OAI´s sandwich nanoparticle immunoassay (capture antibody Y; analyte ●; fluorescent detection antibody Y).

RESULTS

Functionalised nanoparticles, capture and detection anti-protein A antibodies were incubated with increasing concentrations of protein A. Higher concentrations of the analyte favour the formation of sandwich complex. As a result, the amount of bound detection antibody and the molecular brightness of the nanoparticles increase. Both parameters give complementary information on the antigen-antibody interaction. FIG.4 shows the number of bound detection antibodies plotted against the protein A concentration.

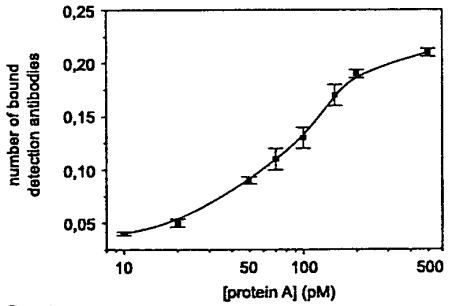

FIG. 4 Typical binding curve of the quantitative protein A assay

The principle of multiple-binding site assays as described in the above nanoparticle immunoassays example may also be applied to assays working with membrane derived vesicles targeting membrane integrated receptors.

REFERENCES

1. Schaertl S. et al. A novel and robust homogeneous fluorescence-based assay using particles for pharmaceutical screening and diagnostics. J Biomol Screen 2000; 200: 227.
2. Kask P. et al. Fluorescence-intensity distribution analysis and its application in biomolecular detection technology. Proc Natl Acad Sci USA 1999; 6: 13756.
3. Rüdiger M. et al. Single-molecule detection technologies in miniaturised high throughput screening: binding assays for G protein-coupled receptors using fluorescence intensity distribution analysis and fluorescence anisotropy. J Biomol Screen 2001; 6: 29.

FIDA technology is covered by pending patent applications

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cFLA

Fluorescence Lifetime

Highly Sensitive Antenna with Nanosecond Resolution

evotec OAI

cFLA provides insight into changes of the electronic structure of a certain fluorescent molecule and its micro-environmental interaction with nanosecond time resolution.

Fluorescence lifetime (T_f) is defined by the mean time, the fluorophore spends in the excited state (S_1) before returning to the ground state (S_0). The competition of fluorescence emission with other de-excitation processes strongly depends on environmental and conformational effects on the tagged fluorophore (FIG. 1). Therefore, the measure of the fluorescence lifetime of a certain molecular species is a prominent susceptible parameter and can be applied for a wide range of multiple biomolecular interactions.

Combining lifetime analysis with confocal optics opens the possibility for miniaturised, homogeneous assay formats. The avoidance of any separation steps enables biomolecular studies under real thermo-dynamic conditions. The nanosecond time resolution allows the use of conventional, prompt-fluorescent dyes.

KEY APPLICATIONS

- low affinity interactions
- FRET applications: extended distance range
- multiplexing applications

KEY FEATURES

- high statistical accuracy: short measuring times (< 1 second)
- wide concentration range: sub-nanomolar to millimolar concentrations of fluorescent species
- high precision: very sensitive to small environmental changes and thus in lifetime
- ease of use: conventional dyes covering the entire visible spectrum can be applied

TECHNOLOGY PRINCIPLE

Subject of fluorescence lifetime analysis is the distribution of the time interval between the excitation pulse and the detection of fluorescence photons, measured for a large number of pulses.

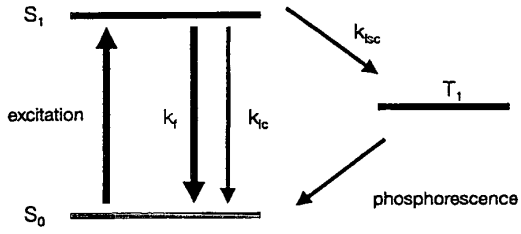

FIG. 1 Jablonski energy diagram illustrating the main depopulation processes of the excited state. Fluorescence relaxation (k_f) is primarily competed by non-radiative processes: conversion into the first triplet state, T_1 by intersystem crossing (k_{isc}) and internal energy conversion (k_{ic}).

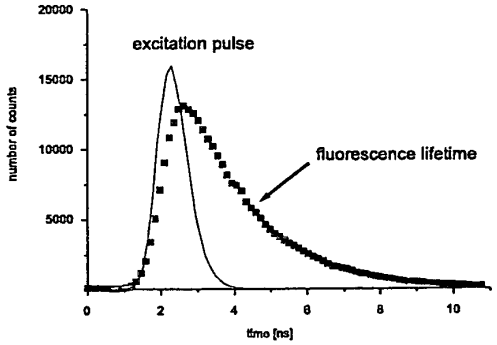

FIG. 2 Fluorescence lifetime decay histogram and corresponding laser excitation pulse. It plots the number of photons detected in a certain time interval after excitation.

READ OUT

Resolution of multiple fluorescent species:

- fluorescence lifetime τ_f
- amplitudes proportional to the product of concentration (c) and molecular brightness (q) (fractional intensities)

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evotec OAI

APPLICATION

Calmodulin is a regulatory protein involved in a variety of Ca^{2+}-dependent cellular signal pathways. Two similar domains with two Ca^{2+} binding sites each are identified. In solution both domains are connected by a flexible linker. Upon binding of Ca^{2+} those residues that create the binding site for most target proteins become exposed to the molecules surface.

RESULTS

A target peptide, whose C- and N-terminus are the predominant interaction sites for the binding of calmodulin, was tagged with a fluorescent dye at the C-terminus. The fluorescently labelled peptide was incubated with increasing calmodulin concentrations at room temperature for 10 min prior to measurement. Binding of calmodulin to the C-terminus of the peptide changes the microenvironment of the dye thus influencing its fluorescence lifetime. The changes in fluorescence lifetime due to the increased calmodulin concentration are plotted (FIG. 2).

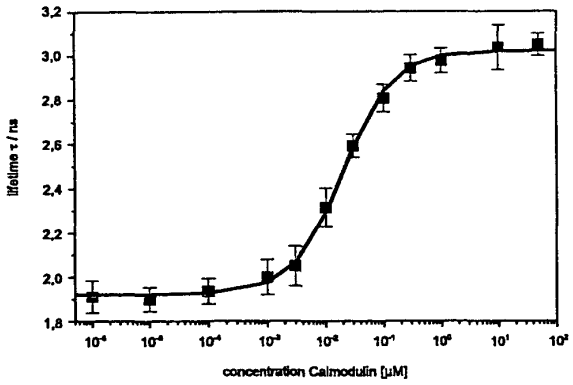

FIG. 2 Calmodulin-peptide interaction pictured by the change in fluorescence lifetime due to increasing calmodulin concentration.

The fluorescence lifetime decay histograms shown in FIG. 3 visualise the influence of calmodulin binding on the fluorescence lifetime of the fluorescently labelled peptide. Binding of calmodulin results in a noticeable longer decay (blue curve) compared to the lifetime decay of the unbound peptide (black curve).

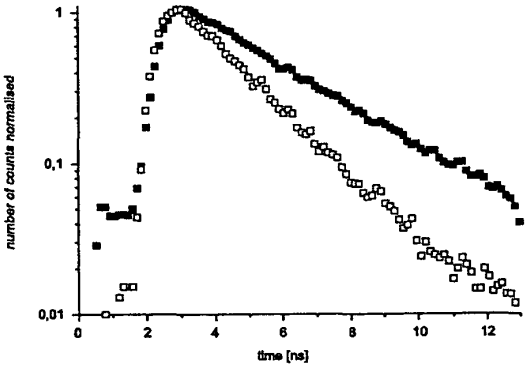

FIG. 3 Fluorescence lifetime decay histograms (detected after excitation) of fluorescently labelled peptide with different calmodulin concentrations.
□: 0 nM calmodulin; 0 % binding
■: 50 _M calmodulin; 80 % binding

REFERENCES

1. Turconi S. et al. Developments in fluorescence lifetime-based analysis for ultra-HTS. DDT 2001; Vol. 6, No. 12 (Suppl.)
2. Auer M. et al. Fluorescence correlation spectroscopy: lead discovery by miniaturised HTS. Drug Discovery Today 1998; 3: 457.
3. Rigler R. Fluorescence correlations, single molecule detection and large number of sceening - Applications in biotechnology. Journal of biotechnology 1995; 41: 177.
4. Rigler R. et al. Interactions and Kinetics of Single Molecules as Observed by Fluorescence Correlation Spectroscopy New Methods and Applications. Springer Verlag 1992; 13-24

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DETECTION FLUORESCENCE

FCS

Molecular Motion

New Insight into Dynamical Processes with Molecular Resolution

evotec OAI

FCS forms the cornerstone of a new generation of single molecule fluorescence based detection technologies. It measures the translational diffusion of individual fluorescently labelled molecules (FIG. 1) and is capable of distinguishing two or more molecular species (FIG. 2). The confocal detection volume used for FCS makes it ideally suited to miniaturisation of the sample volume. Volumes as small as one microlitre can be handled easily.

The translational diffusion behaviour of molecules strongly depends on their mass and shape. Thereby, FCS is an ideal tool to analyse a broad range of biomolecular interactions such as bimolecular binding reactions, catalytic cleavage processes, assembly of multimeric complexes from their subunits [1-3].

KEY APPLICATIONS

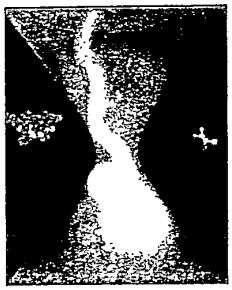
- protein analysis: receptor-ligand, antigen antibody, protein polymerisation, protein-DNA, (substitution of gel-shift assays)
- DNA / RNA analysis: hybridisation kinetics, mutation analysis, quantitative PCR, genotyping (GALIOS™)
- micellar systems: CMC determination of detergents, protein binding to liposomes

KEY FEATURES

- molecular resolution: multiple fluorescent species can be distinguished
- molecular motion: probing of properties such as diffusion coefficients, molecular mass and viscosity
- ns-time resolution: probing of time constants of chemical reactions, e.g. photophysical processes such as triplet state, photobleaching

TECHNOLOGY PRINCIPLE

Each fluorescent molecule that diffuses through the confocal detection volume gives rise to a burst of fluorescence photons. The length of each photon burst allows differentiation between faster and slower diffusing particles.



small particles:
fast diffusion

large particles:
slow diffusion

FIG. 1 Diffusion of fluorescent molecules through a confocal detection volume

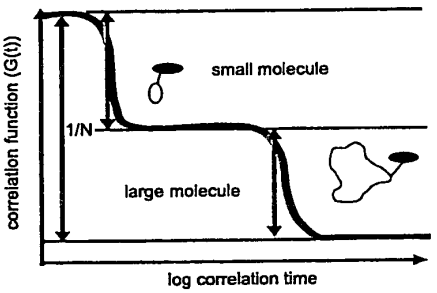


FIG. 2 Schematic graph of a multi-component autocorrelation analysis

READ OUT

Single molecule resolution of multiple molecular species:

- translational diffusion time τ_D
- number of particles N

Photophysical process:

- triplet time and triplet fraction

Secondary data evaluation:

- Diffusion coefficient $D \sim \frac{1}{\tau_D} \sim \frac{1}{\sqrt[3]{M_r}}$

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APPLICATION

The use of detergents is frequently an important aspect of the assay development process. Detergents are used to suppress adhesion and nonspecific binding to probe cubes or sample carriers. Additionally, they may contribute to specific interactions between the reaction partners under study.

In the application presented here FCS is used to define the ideal concentration range for detergents during assay development and to specify the CMC (critical micelle concentration) under particular assay conditions[4].

Fluorescently labelled peptides were analysed in the presence of increasing detergent concentrations. FCS measurements at each detergent concentration yielded the following results: At low detergent concentrations, the loss of peptide molecules by adhesion to surfaces is measured by a decreasing number of particles, (FIG 3 (A)). High detergent concentrations affect the formation of micelles, in which fluorescent molecules could be embedded[2]. This results in increased diffusion times (FIG 4) and reduced fluorescence intensity (FIG 3 (C))

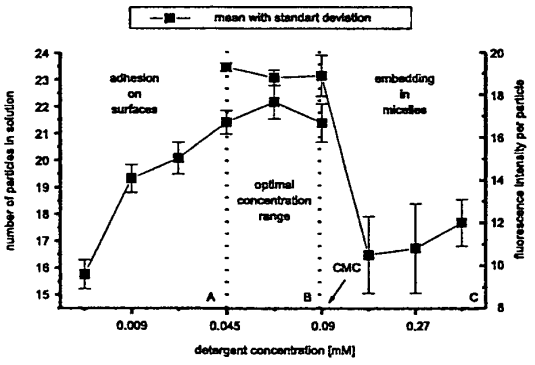

FIG. 3 Influence of increasing detergent concentration on the number of particles and the fluorescence intensity per particle.

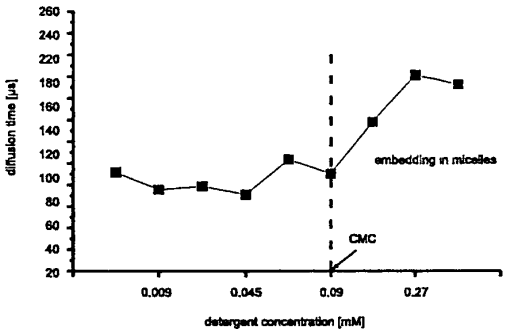

FIG. 4 Influence of the detergent concentration on the diffusion time.

CONCLUSIONS

These experiments indicate that the ideal concentration of the tested detergent for assay development lies between 0.045 and 0.09 mM. The CMC of the detergent under study was later experimentally determined to be 0.09 mM.

REFERENCES

1. Rigler R. Fluorescence correlations, single molecule detection and large number of sceening-applications in biotechnology. Journal of biotechnology 1995; 41: 177

2. Meseth U. et al Resolution of Fluorescence Correlation Measurements. Biophysical Journal 1999; 76: 1619.

3. Auer M. et al. Fluorescence correlation spectroscopy: lead discovery by miniaturised HTS. Drug Discovery Today 1998; 3: 457.

4. Ghosh M. et al. Interfacial and Micellisation Behaviours of Binary and Ternary Mixtures of Amphiphiles (Tween-20, Brij-35 and Sodium Dodecyl Sulfate) in Aqueous Medium. J Colloid Interface Sci 1998; 2: 357.

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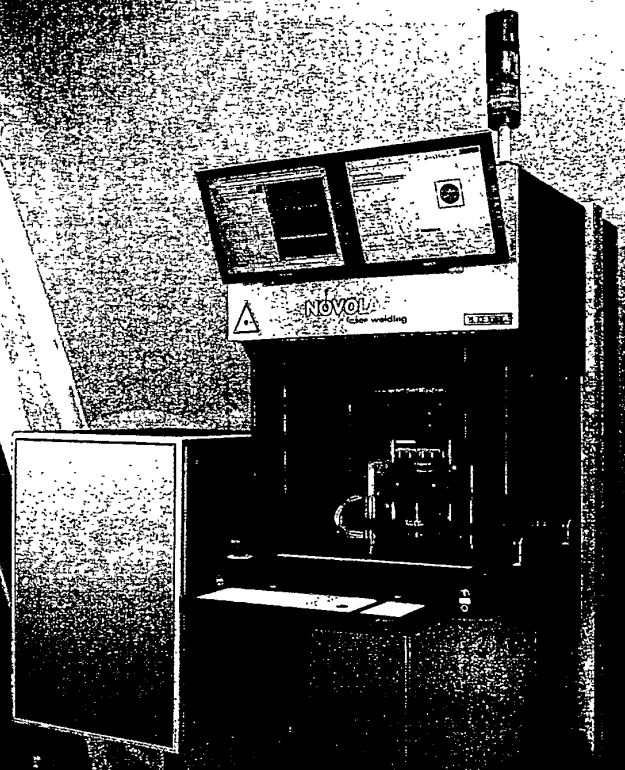
NOVOLAS p

laser welding



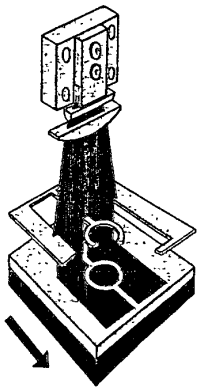
Lasersystems for Plastic Welding

Precision Welding for Micro Components

Lasersystems

NOVOLAS µ
laser welding

Mask Welding with NOVOLAS µ



The concept of **Mask Welding** is based on the principal of **Transmission Welding**: A line, or curtain, of laser light sweeps over a customer defined mask pattern. The components are precisely joined where the laser is allowed to pass through the mask.

The precision of the mask design and software controlled laser power allow for the assembly of microstructures with weld lines as narrow as 100 µm. Covered areas are not exposed to thermal stress. Though the mask process is perfect for high-speed production, the mask can be easily changed allowing for production flexibility.

Technical Information

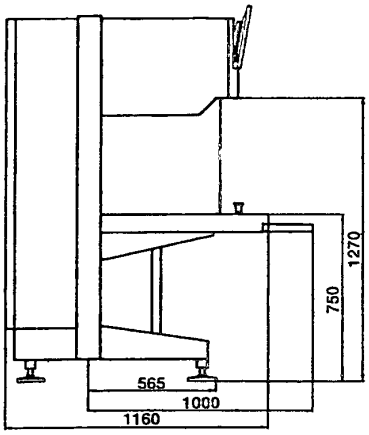
An intelligent **Adjustment System,** incorporating a state-of-the-art **Vision System,** provides for precise alignment of the parts and mask.

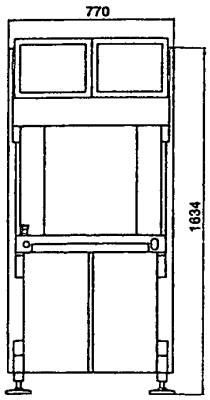
The graphical user interface of the control software, µ-WIN, provides graphical visualization to assist in the setting of parameters.

The NOVOLAS µ Systems were ergonomically designed to simplify handling and allow for increased throughput. The system is suitable for clean-room-conditions.

Customized masks, manufactured by a photolithographic process, are available as requested.

Dimensions in mm





Laser Type	High Powered Diode Laser
Laser Power Output	90 W
Image Processing	Optical
Max. Component Size	110×50×30 mm
Max. Welding Area	110×50 mm
Top Comp. Thickness	2 mm
Axis	9 Step Motors
Clamp Device	Pneumatic
Control	PC Control for Laser and Axis, Process Control
Line Voltage	230 VAC +/- 10% (optional 200 VAC) (Single phase with ground contact / Short Prot. 16A)
Frequency	50 / 60 Hz
Current Consumption	Max. 10 A
Air Pressure	Min. 6 bar, ¼" Tube
Cooling	Air stream, Exhaust Air max. 130°F (55°C)
Environment Conditions	60-105°F (15 –40°C)
Weight	1450 lb (ca. 650 kg)
Laser Class	1
CE conform	
Technical data subject to change	
Further options on request	

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Microfluidic Tool Kit (μTK)

The Solution for Microfluidics R&D

Leader in Microfluidics

Micralyne is a world leader in the design and fabrication of microfluidic glass chips. To facilitate the use of our chips we have developed a complete tool kit (μTK) to help our customers get up and running quickly. This low cost solution is designed to be easily set up, programmed, and reconfigured. The operator can use the instrument for applications ranging from proteomics to generic chemical analysis.

What is it?

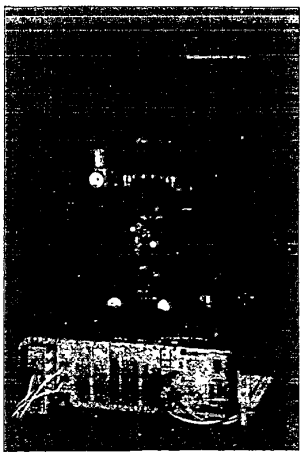
The μTK is comprised of the following components: HV electronics, optical detection electronics, software control, detection optics, compiled LabView interface, stage and chip. The user inserts a chip loaded with sample and reagent, enters a voltage program into the software, and runs the experiment

Modular Design

The system and software are modular in design and allow for rapid reconfiguration for new applications. Micralyne can assist in the development and support of software and custom microfluidic chips for users wishing to explore new fields. This modularity allows the user to tailor the operation and performance of the kit to suit their specific requirements.

Easy to Use

This system provides a convenient option for researchers who are involved in the development of microfluidic chips and related applications in the fields of chemistry, biology, and life sciences. The system integrates all aspects of the development phase such that the user need only unpack the kit, provide reagents, and a procedure. High performance, small size, low cost, and ease of use are key features of the Microfluidic Tool Kit.



μTK

MICROFLUIDIC TOOL KIT

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Components

- **Diode Laser** with either:
  - 635 nm LIF detection for Cy5-labelled species, or 532 nm LIF detection for rhodamine labelled species
  - appropriate filters for chosen laser/dye set
- **Epiluminescent Confocal Microscope**
  configurable for both:
  - visual inspection with an eyepiece
  - detection using a Hamamatsu H5773-03 PMT, with 16-bit data acquisition
- **Electronic Control Module**
  - based on a 68332 microprocessor
- **Dual Channel High Voltage Modules**
  - two 6 kV channels per module
  - modules either dual positive or dual negative
  - maximum of 4 modules (8 channels) per instrument
  - can be set up in two ways:

  One HV channel per electrode

  (one board controls two electrodes)
  - fast relay switching between HV,floating, and ground
  - slightly slower switching between two different HV settings.

  Two HV channels per electrode

  (one board controls one electrode)
  - fast relay switching between HV1, HV2, floating and ground.
- **Standard Microfluidic Chip**
- **Compiled Labview Interface**

Future Options

- **Electrochemical Detection Module**
  - dedicated chips having embedded electrodes
- **Single Zone Temperature Control**
  - plus 5°C to plus 95°C range

Requirements

- Pentium 300MHz PII, 128 MB RAM, 2GB HDD, Win95/98/NT

For more information, contact Micralyne at uTK@micralyne.com

EDS204, Rev.010-391

Leaders in Microfabrication

Since 1988, Micralyne has been designing and fabricating miniaturized devices using microfabrication technologies. Our expert staff, along with our extensive manufacturing and Q.A. processes, allow us to fabricate parts of extremely high quality and precision.

Silicon and Glass Microchips

Micralyne's chips are created using wet chemical, electrochemical, and plasma etching techniques. Bio-compatable electrodes can also be embedded into the chips at the request of the customer. These chips are used by our clients in a variety of applications such as separation using capillary electrophoresis, multi-channel electrospray, and cell manipulation and filtration.

Sensors and Actuators

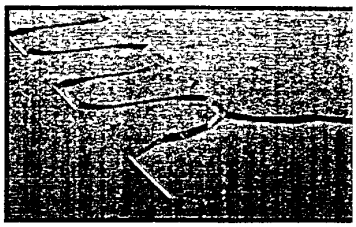
Our sensors and actuators are constructed using various transducer technologies including piezoelectric, piezoresistive, capacitive and electrochemical processes. The resulting devices can be used in instruments such as accelerometers, silicon based microphones, magnetic field sensors, and electrochemical sensors.

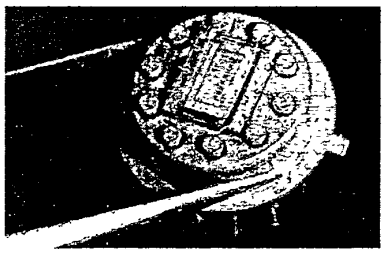
Metalized Substrates

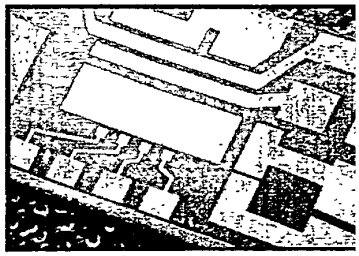
We metalize aluminum nitride, synthetic diamond and silicon substrates using sputtering and photolithography techniques. Thin film metallization has a variety of applications in multichip modules, laser submounts and high performance heat spreaders.

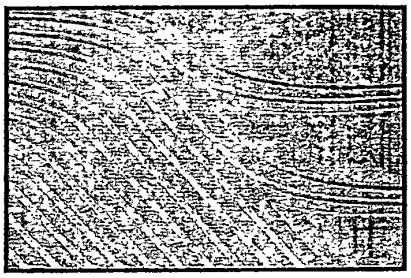
Optical and Optoelectric Devices

Our optical and optoelectric components are fabricated using a broad range of techniques depending on the desired results. These methods include photolithography, RIE etching, PECVD, and sputtering. Some examples of the resulting devices are planar waveguides, optical interconnects, and fiber connectors.









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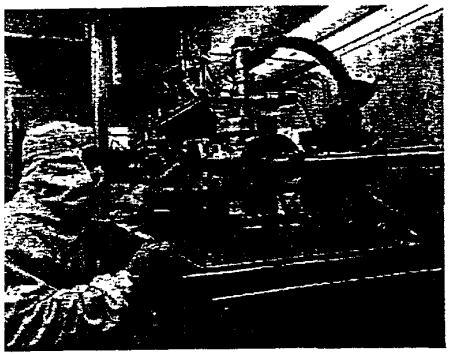
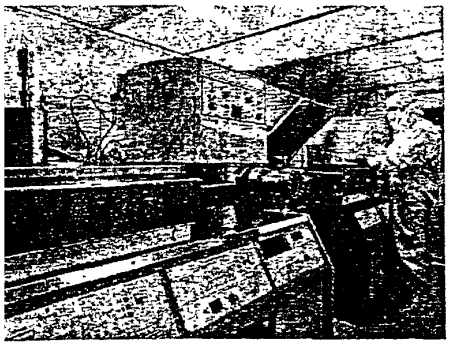
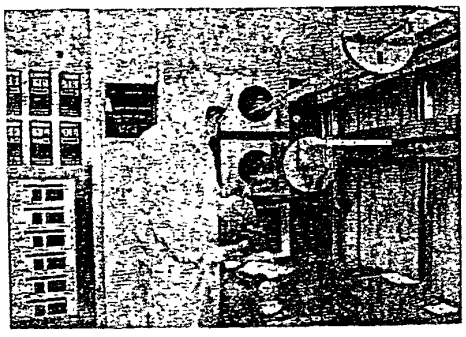


Advanced Equipment and Facilities

Micralyne has a state-of-the-art 40,000 sq. ft. facility that includes microfabrication labs and extensive cleanroom space. These modern facilities help our staff to conduct leading-edge R&D and custom manufacturing for our clients.

- four Perkin Elmer 4410 sputter systems (3 targets per system).
- sputtered materials: Ti, W, Ta, Pt, Au, Cr, NiCr, Al, Ag, Cu
- three contact mask aligners for photolithographic patterning.
  - two Karl Suss systems for 4 inch wafers
  - OA system which provides 6 inch wafer capacity
  - one system is equipped with front to backside align ment capability.
- Plasmatherm 790 PECVD deposition system (SiO_2, SiN, a:Si)
- Plasmatherm 790 Reactive Ion Etcher with 10 inch chuck
- Plasmatherm Batchtop Reactive Ion Etcher with 7 inch chuck
- four evaporation systems including e-beam and thermal
- large wet deck areas for etching metals and dielectrics
- energy dispersive x-ray analysis
- scanning electron microscope
- surface profilometer
- thin film stress tester
- spectrophotometer
- ellipsometer





Off-The-Shelf Chips For CE

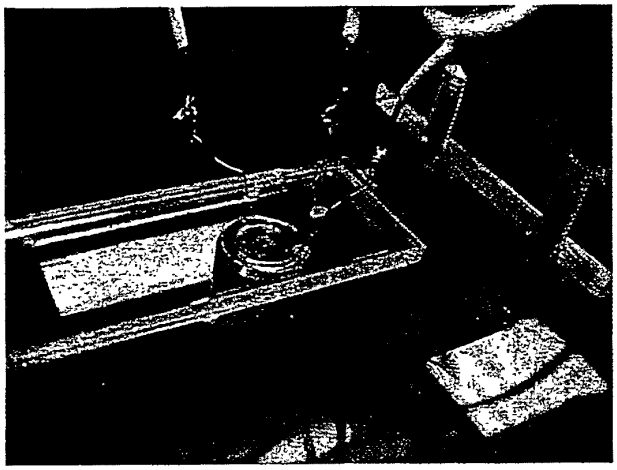
Micralyne Standard Fluidic Chips

Micralyne, a leader in the design and fabrication of custom-designed microfluidic devices, is now offering a series of Standard Microfluidic Chips

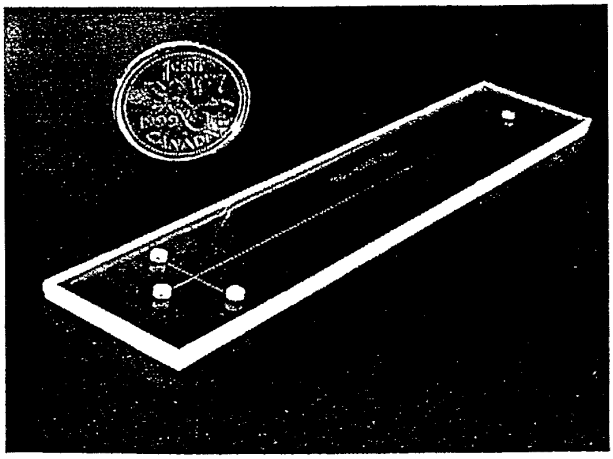
These chips feature simple designs for single sample injection, and are ideally suited to a wide variety of chemical and biochemical analyses by means of capillary electrophoresis with laser-induced fluorescence.

Due to larger fabrication volumes, our generic chips are more economically priced and available off-the-shelf for rapid delivery. For further details, please contact Micralyne at (780) 431-4400 or by e-mail at chips@micralyne.com.

- *Standard Microfluidic Chips are form-fitted for Micralyne's Microfluidic Tool Kit (μTK) an instrumentation support platform (see Microfluidic Tool Kit information sheet).*



A Standard Microfluidic Chip operating in a capillary electrophoresis instrument using laser-induced fluorescence detection.



A Twin T 100 μm Standard Microfluidic Chip.

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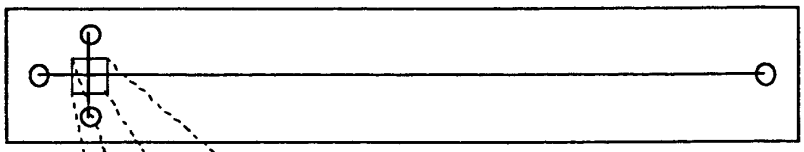
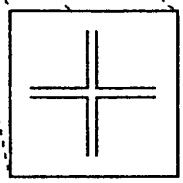
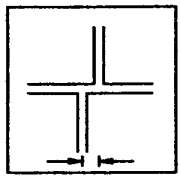
Designs and Dimensions



Two designs are available relating to different injector designs: simple cross and twin T-100 mm.

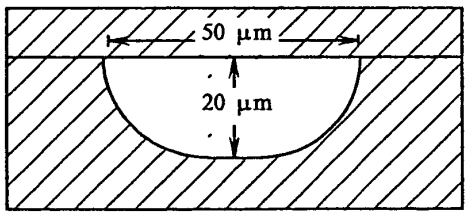


Simple Cross
MC-BF4-SC



100 μm Twin T
MC-BF4-TT100

Chip Format:	16mm x 95mm x 2.2mm channel plate thickness of 1.1mm cover plate thickness of 1.1mm
Material:	Low fluorescence Borofloat glass from Schott Optical Glass
Channel Cross-Section:	Cross-section is approximately semicircular



Channel Dimensions[1]:	Separataion Channel Length: 85.0mm (80.0mm from intersection) Injection Channel Length: 8.0mm
Access Hole Diameter:	2.0mm ± 0.1mm

Prices[2]:	Number of Chips	2	10	50	100
	Cost Per Chip ($US)	$210	$195	$180	$160

[1] Access hole diameter is not included in channel lengths

[2] Prices do not include shipping charges

micralyne

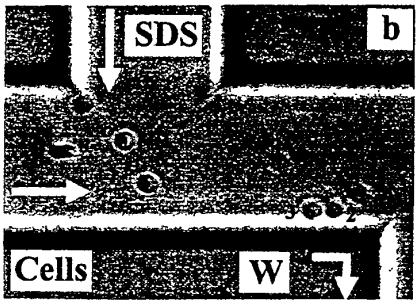
Microfluidic Chip Capabilities

Background

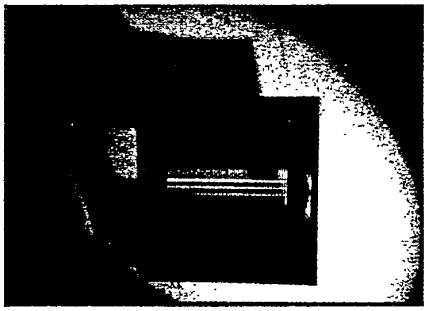
Micralyne has been a leading manufacturer of microfluidic devices for commercial and research applications since 1992. Our work in microfabrication has gained international recognition among clients in Europe, Japan, the United States, and Canada. We have made many of the seminal devices for pioneers in μTAS and genetic analysis such as Drs. Jed Harrison, Andreas Manz, Fred Regnier, and Daniel Figeys; as well as, corporations such as PE Biosystems, Lynx Therapeutics, and Aclara BioSciences.

Over the past several years, we have developed a wide range of capabilities and fabrication technologies for microfluidic devices. Core technology developed at Micralyne consists of micromachining channels, chambers, filters, solid supports, and embedded electrodes onto silicon, glass and quartz substrates.

Specific applications for these devices often include chromatography, high throughput screening, DNA sequencing, protein analysis, cell manipulation, cell filtration, PCR, and multichannel electrospray ionization.



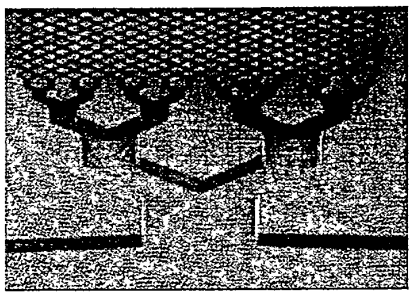
Harrison, D.J., Li, P.C.H., Analytical Chemistry, 69, 156-1568, (1997).



Crabtree, H.J., Kopp, M.U.,Manz, A., Analytical Chemistry, 71, 2130 - 2138 (1999).

Our Role

With experienced scientists and engineers on staff, Micralyne can fine-tune its involvement in your work to help realize your microfabrication objectives. Our role can range from participation in a joint, collaborative research venture to full-scale production. Very often, these different roles can be seen as progressive phases in Micralyne's relationship with you, the client.



He,B., Regnier, F., Tait, N. Analytical Chemistry, 70, 3790-3797 (1998).

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Guidelines for Custom Fabrication

Micralyne has broad microfabrication capabilities, ranging from the etching of various substrates, to the embedding of electrodes on-chip. We are uniquely positioned to work with our clients and partners from the earliest stages of device development through to volume manufacturing.

Design:

· hand drawings, computer schematics, or design files (.dxf, .dwg, .tdb, .gds) are acceptable

Substrates:

· Si and quartz : 3" - 4" wafers
· Corning 0211 glass : 3" - 6" plates
· Schott Borofloat glass : 3" - 6" plates

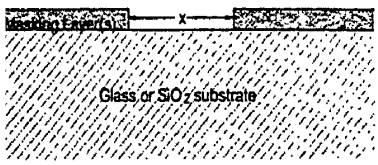
Cover Plate, Bonding, Dicing:

· ultrasonically-drilled holes, diameter ≥ 300 µm
· fusion bonding of glass and quartz devices
· anodic bonding of Pyrex on Si
· automated wafer/device dicing

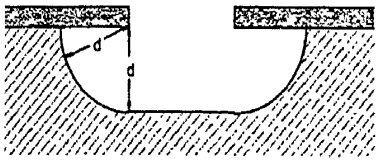
Etching:

Isotropic

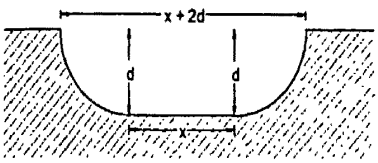
Window in masking layers before etching



otropic etch to form "D"-shaped channel cross-section

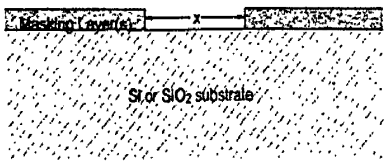


Post-etch dimensions of channel cross-section

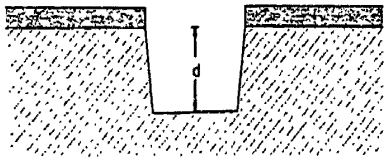


Reactive Ion Etch (RIE)

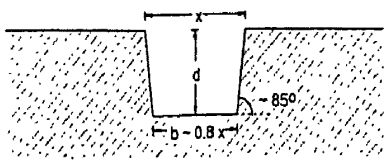
Window in masking layers before etching



Reactive Ion etch to form channel with ~ vertical sidewalls

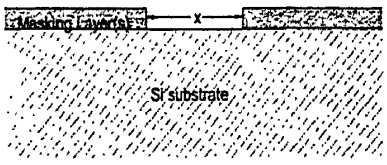


Post-etch dimensions of channel cross-section

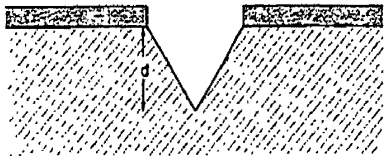


Anisotropic

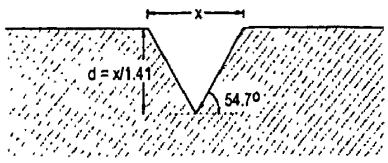
Window in masking layers before etching



Anisotropic etch to form "V"-shaped channel cross-section



Post-etch dimensions of channel cross-section



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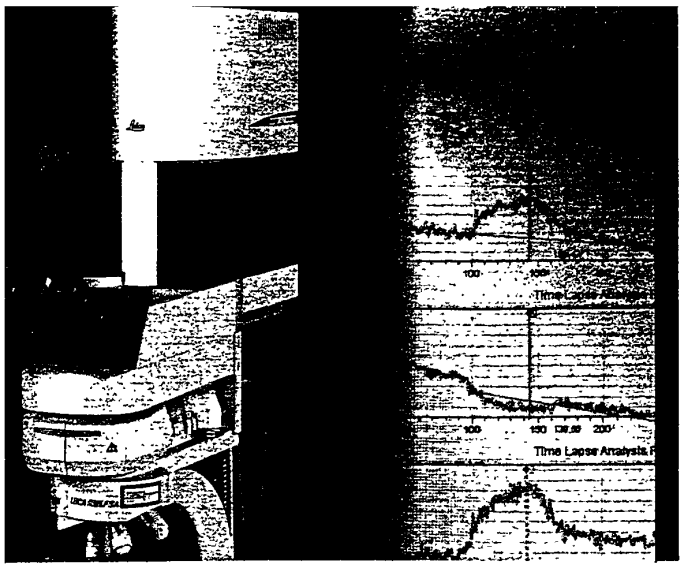
附件二、 德國 Leica 公司相關資料



Leica TCS SP2 RS

Fast Confocal & Multiphoton Scanner

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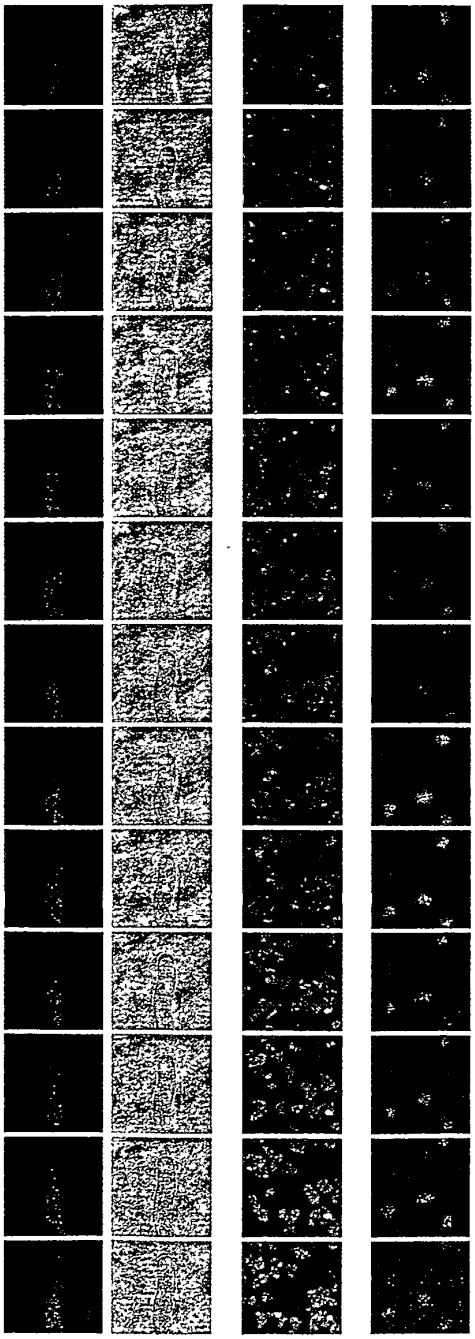
Leica TCS SP2 RS: Fast Confocal & for the study of high speed event dyn



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- no loss in speed for multi-color recording
- up to 4 simultaneous confocal fluorescence detectors
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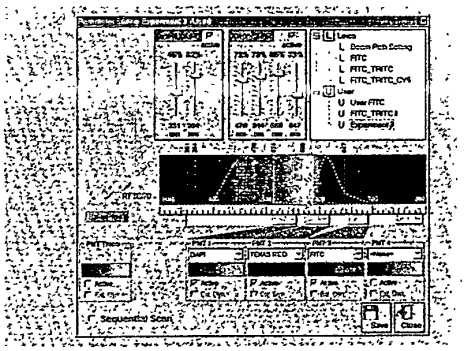
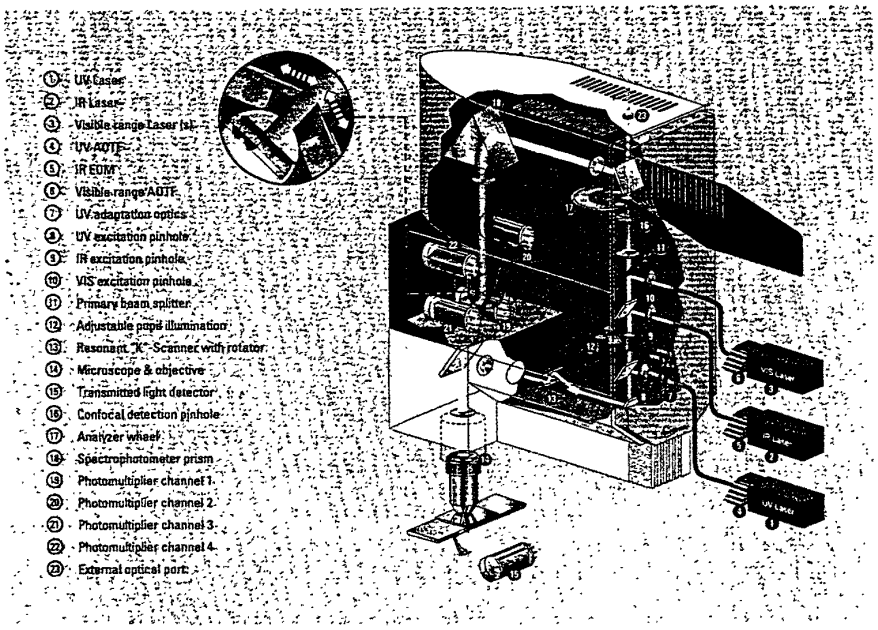


Spectral Detector Interface

& Multiphoton Scanner

namics



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Further Information, Dimensions and Installation Requirements: see Leica TCS SP 2 brochure

Leica TCS SP2 RS Specifications

(including optional items)

Microscopes:	• Upright fixed stage: DM LFS A, upright: Leica DM R, RE, RXE, RXA • Inverted: Leica DM IRB, IRBE
Z drive:	• Precision focusing nosepiece (DM RXE): 2 mm travel, 10 nm resolution • High-resolution z stage: 170 micrometer travel, xyz: 40 nm resolution, xz: <1 nm resolution • Internal motorization of Leica DM LFS A, RE, RXE, RXA, IRBE
Lasers & Attenuation/ switching modules	• Ar UV 50 mW 351, 364 nm • HeCd 40 mW 442 nm • Ar 100 mW 457 nm, 488 nm, 514 nm • ArKr 75 mW 488nm, 568 nm, 647 nm • Kr 25 mW 568 nm • HeNe 1.2 mW 543 nm • HeNe 10 mW 633 nm • Ti:Sapphire, ps/fs versions, 720-1000 nm • AOTF 4 or 8 channels, visible range • AOTF, UV range • EOM, IR range (MP) • Merge module for 4 lasers
Confocal Unit:	Optics: • User-switchable between Leica microscopes • Alignment-free for lifetime • 3 individual ports for external lasers for up to 6 lasers connected simultaneously • Fiber-coupling and/or direct coupling of multiphoton lasers to confocal unit • Spectral range of detector optics: 400 - 850 nm • UV and MP possible in one system • Field-upgradable to MP microscopy • UV system with individual objective correction lenses • Adjustable pupil illumination • Optical Port for external devices • One pinhole, variable diameter size Scanner: • X scanner with two independent galvanometers • Line frequency: up to 8000 lines/s • Frame rates: ... • Scan resolution: up to 1024 x 1024 pixels • Scan zoom 1 - 8 x • Scan rotation -5 to +95 degrees

Lines/frame	Max no of simultaneous detector channels	8 bit signal digitization	12 bit signal digitization	Lines/frames/s (bi-directional scan)	Lines/frames/s (uni-directional scan)
1 (32768 lines/ frame xt mode)	8	X	X	8000 lines/sec	4000 lines/sec
128	8	X	X	20 frames/s	10 frames/s
256	4	X	X	8.4 frames/s	4.7 frames/s
512	2	X	X	7.2 frames/s	3.8 frames/s
1024		X		5 frames/s	2.5 frames/s
1024	1	X	X		2.5 frames/s

Leica TCS SP2 RS Specifications

(including optional items)

Confocal Unit	Detectors: • Highly sensitive spectral detector, 1 - 4 simultaneous channels • Continuously adjustable bandwidth and center wavelength • Spectral steepness factor < 1 • Low-noise photomultipliers • Up to 12 bit digitization per channel • Transmitted light/DIC detector • Non-descanned dual channel transmission detector (MP) • Non-descanned dual channel reflection/fluorescence detectors (MP)
Electronics	• Scanner control with FPGA (Field-programmable gate arrays) • Trigger-in/out ports • 8 detector channels, 12 bit digitization, simultaneous (see table on reverse side) • Ultra-wide SCSI interface to PC • High-performance PC workstation • One or two monitors
Software	• Fully operator-configurable user interface • Intuitive and guided • Context-sensitive online help system • Multi-dimensional series aquisition • Supported by direct-access digital control knobs • Region of interest scan • Excitation multiplexing • Emission spectrum recording • Time-lapse recording • Surface reconstruction • Multiple measurement functions • Physiology software • Multi-color software • 3D software with multiple reconstruction & rendering functions • Macro developer software

Abbreviations:
MP = Multi photon microscopy
UV = Ultraviolet microscopy
AOTF = Acousto-optical tunable filter
EOM = Electro-optical modulator

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SCIENTIFIC AND TECHNICAL INFORMATION
Special issue "Confocal Microscopy", CDR 4, pp. 4–14, October 2000

A confocal microscope with spectrophotometric detection

by C. B. Calloway, Leica Microsystems Inc., Exton, PA, USA

Design and function

The Leica TCS SP and SP2 Confocal Microscopes combine spectrophotometric detection with confocal microscopy. The result is a multi-channel confocal imaging spectrophotometer that significantly increases the flexibility and efficiency of the detection system.

In conventional point scanning confocal microscopes excitation light from laser(s) is delivered to the scan head via fiber optic, passed through a pinhole, reflected by a primary dichroic to the scanning system, and scanned onto the surface of the specimen. Light emitted from the specimen is descanned and passed to the detection system. The detection pinhole(s) are placed either between the primary dichroics and the detection system as in Leica confocal microscopes or closer to the end of the detection system. In the detection system emitted light is separated using a combination of dichroics, mirrors, and barrier filters before being passed to the photomultiplier detectors.

The Leica TCS SP/SP2 Spectral Confocal microscope has the same beam path as the filtered system up to and including the detection pinhole. The detection system including the secondary dichroics and the barrier filters is replaced by the spectrophotometer detection system (SP) (Fig. 1). The light emitted from the focal plane that passes through the detection pinhole has both intensity and spectral information. In the SP system this light is passed through a prism. The prism splits the emitted light into a spectrum from 400 to 750 nm. The spectrum is directed at a PMT for detec-

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

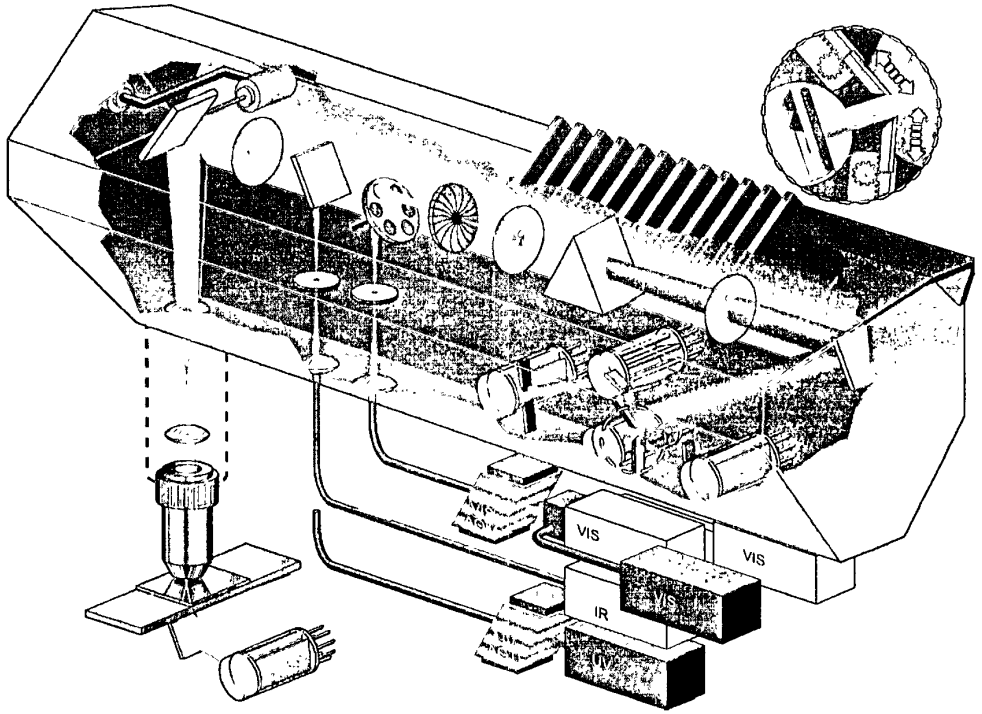

Fig. 1: Schematic illustration of the beam path in the Leica TCS SP. The prism splits the beam into its spectral components. The enlarged detail shows the detector system with the motorised slit plates, which can be opened and closed.

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A confocal microscope with spectrophotometric detection (continued)

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tion. The physical dimension of this spectrum is such that the entire spectrum can be imaged onto the window of the PMT. In front of the PMT is a slit. The slit is capable of two movements with respect to the spectrum:

1) The slit can be widened or narrowed to include a larger or a smaller part of the spectrum, i.e. the bandwidth of the light passing through the slit can be made narrower or wider. This is analogous to changing the width of a barrier filter continuously while scanning.

2) The slit can be moved across the spectrum, i.e., the center of the detected bandwidth can be moved continuously across the spectrum. This is analogous to creating custom barrier filters anywhere in the spectrum and allows for wavelength scanning of images (lambdascan)!

A system with one slit and one detector is a single channel confocal imaging spectrophotometer. However, the TCS SP is designed to work with up to four detectors as follows. In the single detector system described above, the spectrum of emitted light is directed at a PMT and the slit in front of the PMT is positioned to include only a particular bandwidth of the spectrum. The remainder of the spectrum is excluded by the plates on each side of the slit (Fig. 1, detail). Wavelengths shorter than those collected by the slit are rejected by the plate on one side of the slit and wavelengths longer than those collected by the slit are rejected by the plate on the opposite side of the slit. In the SP detection system the surfaces of the two plates of the slit are mirrored and are angled to reflect the rejected portions of the spectrum off to other detectors. These detectors, like the detector described above, have slits that can be positioned to include only a particular bandwidth of the spectrum rejected by the first detector.

For example, in a sample containing FITC, TRITC and Cy5 (Fig. 2), the light emitted by

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

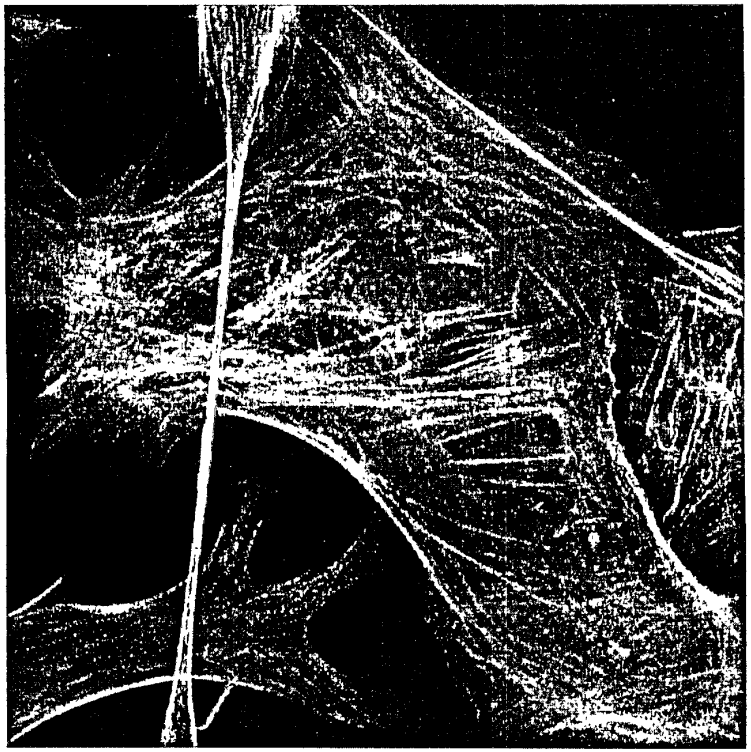

Fig. 2: The fibroblasts have been stained with fluorochromes to distinguish them from different components of the cytoskeleton. The actin fibres labelled with Phalloidin/ FITC appear green. The microtubules (displayed in red) have been stained immunohistochemically with anti-Tubulin/ TRITC. Vimentin fibres (displayed in blue) have been marked with anti-Vimentin/ Cy5.

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A confocal microscope with spectrophotometric detection (continued)

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fluorochromes in the focal plane passes through the detection pinhole to the prism where it is split into a spectrum from 400 to 750 nm. The spectrum is directed at a PMT. The slit in front of the PMT is adjusted to select the wavelengths emitted by TRITC (555–620 nm). The shorter wavelengths emitted by FITC (500–535 nm) are rejected by the mirrored plate on the left side of the slit and reflected to a second detector. The slit in front of the second detector is positioned to select the wavelengths emitted by FITC for collection by the second PMT. Simultaneously the longer wavelengths emitted by Cy5 are rejected by the mirrored plate on the right side of the first slit and reflected to a third detector. The slit in front of the third detector is positioned to select the wavelengths emitted by Cy5 (650–750 nm) for collection by the third PMT. By mirroring the plate in the slit in front of the third detector that rejects the longer wavelengths, longer wavelength emissions can be directed to a fourth detector complete with a slit mechanism. In this way the system can be configured with 1, 2, 3, or 4 detectors that operate simultaneously. Note that the prism in combination with the slits in front of the detectors both split the emitted light between detectors and select the wavelengths to be collected by the detectors. The prism and slit mechanisms thus take the place of the detection dichroics and barrier filters in filtered systems.

Practical advantages

The SP/SP2 spectrophotometer detection system developed by Leica for use with its confocal and multiphoton microscopes represents a revolution in fluorescence detection with significant practical advantages that can be grouped into six broad categories:

1. Flexibility of use: In the SP system the center frequency and bandwidth of detection can be changed during scanning. This is analogous to creating custom dichroics and barrier filters while scan-

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

ning. Consequently, the SP system is capable of detecting the emissions of new fluorochromes without the need to change filters in the detection system. This is a significant advantage in comparison to filter-based systems in which the detection of new fluorochromes requires costly and time-consuming filter changes.

2. Optimal spectral detection: In the SP system the bandwidth of detection can be changed to fit the specific emission of the fluorochrome (Fig. 3). As the bandwidth can be changed while scanning, this is accomplished by adjusting the detection for maximum signal strength. In filtered systems optimization of detection is a two step process: determination of emission spectrum (accomplished outside the microscope) and ordering plus installation of new filters to detect optimally.

3. Optimal spectral separation: In the SP system the cross talk between fluorochromes can be minimized by changing the bandwidth of the detector to exclude the emission of one fluorochrome from that of another (Fig. 4). For example, in a sample dual labelled with FITC and TRITC in which the TRITC is very bright, the TRITC signal is found in the FITC channel because the left shoulder of the emission curve of TRITC extends below 550 nm into the range of wavelengths in which FITC is normally detected (500–550 nm). By adjusting the bandwidth of FITC detection from 500–550 nm to 500–535 nm, the tail of TRITC emission is excluded from the FITC channel. Because the bandwidth of detection can be changed while scanning, the effects of changing the bandwidth on cross talk are immediately visible on image(s) and can be changed interactively. In filtered systems the detection dichroics and barrier filters are in fixed positions and cannot be changed to minimize cross talk.

4. Spectral characterization of emitted light: The SP detection system is a spec-

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

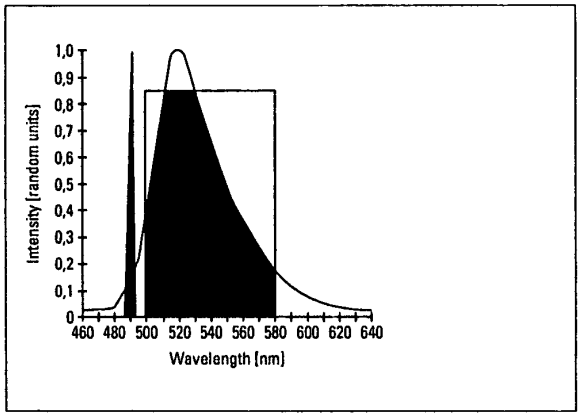

Fig. 3: Schematic illustration to explain the functioning of a detection bandwidth between 500 und 580 nm, which is adjusted to the emission curve of a fluorochrome (black line). The area coloured in green, yellow and red symbolizes the measured emission values. The thin blue curve depicts the excitation spectrum.

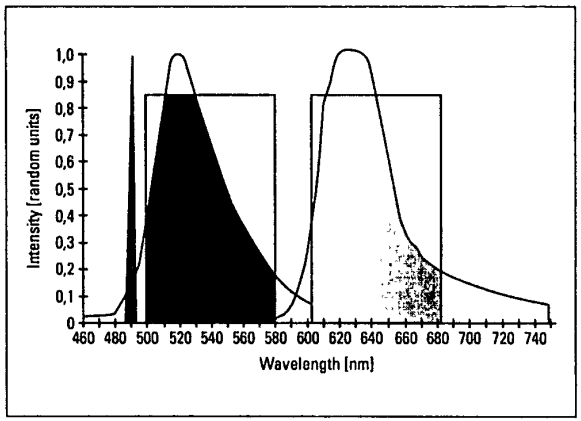

Fig. 4: Two detection bandwidths are adjusted to two different emission curves. To avoid cross talk the detection bandwidths are not positioned one close to the other but with space between them. The thin blue curve depicts the excitation spectrum.

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

trophotometer and thus can be used to characterize the spectrum of light emitted from a sample (Fig. 5). The spectral scanning capability (lambdascan) can be used to determine the emission spectrum of a new fluorochrome to aid in the creation of custom-made detection filters (see #1 above). Another use is the determination of the emission spectrum of a known fluorochrome directly in the sample to use as a guide for optimal detection and separation (see #2 and 3 above) or to determine shifts in emission caused by environmental conditions (pH). Spectral scanning is also a powerful tool for determining the emission spectrum of autofluorescence either for the study of autofluorescence itself or as spectral map for avoiding the autofluorescence.

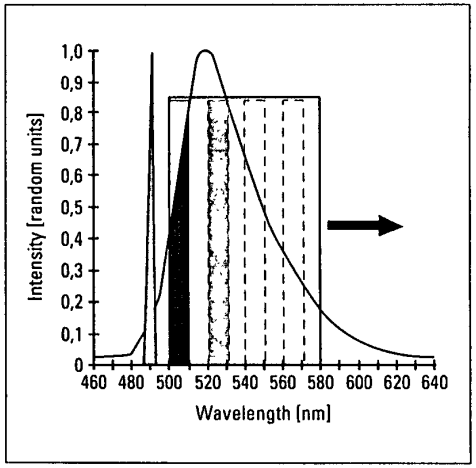

Fig. 5: For a lambda scan the detection bandwidth of a detector is reduced to a width of 10nm and moved over the spectrum to record images. The size of the coloured areas symbolizes the intensity of the emission values measured at the single wavelength segments.

5. Higher transmission of emitted light to the detectors: In filter based systems, the presence of glass filters and dichroic mirrors, often two or three in series, leads to a decrease in the strength of the signal reaching the detectors. The SP detection system lacks these components and thus has a higher efficiency of light transmission to the detectors. Increased signal strength at the detectors is a significant benefit result-

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

ing in brighter, clearer images with less noise. This results in better image resolution (improved signal-to-noise ratio). Significantly, with the higher efficiency of light transmission the amount of laser illumination used to excite the fluorochromes can be reduced thus decreasing bleaching and specimen damage.

6. Ease of use: The interface for the SP detection system is simply a color picture of the spectrum from 400 to 750 nm (Fig. 6). Beneath the spectrum is a nanometer wavelength scale. Beneath the scale are placed from one to 4 sliding bars, which represent the detectors (one bar/detector, to a maximum of four detectors). The position of the bar on the nanometer scale marks the wavelength range of detection. The width of the bar is the bandwidth of the detector. The bars can be moved along the scale and can be widened or narrowed to increase or decrease the bandwidth of detection while scanning. This interface is very easy to use and to understand. In contrast in filtered systems, which offer far less flexibility, the user must understand the usage of a wide variety of filters (i.e., dichroics, band pass, and long pass filters) and mirrors as well as the emission curves of the fluorochromes to optimize detection.

Innovated design of the Leica TCS SP2

In comparison to the previous Leica TCS SP some details in the beam path and electronics of the further developed TCS SP2 have been redesigned. The TCS SP2 system is equipped with three laser couplings so that the microscope can be operated simultaneously with a visible light laser, UV laser and an additional IR laser for multiphoton microscopy applications. Beam expansion optics enable the adjustment of the beam diameter to the different entrance pupils of objectives. Compared with the TCS SP the scan field is enlarged to a diameter of 22 mm. The newly developed K-Scanner,

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A confocal microscope with spectrophotometric detection (continued)

by C. B. Calloway

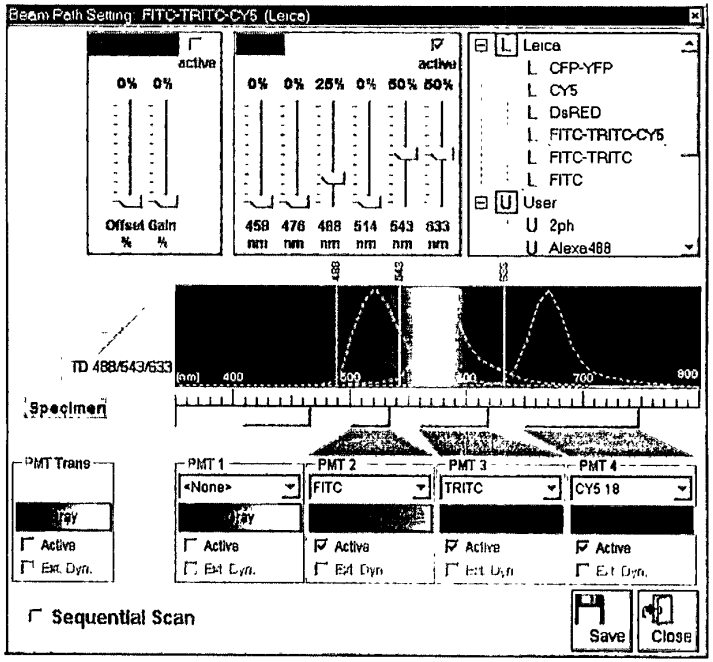

Fig. 6: The user interface of the Leica Confocal Software LCS enables the user-convenient setting of the spectrophotometer parameters. In the middle of the dialog used for this purpose the entire spectral detection range is depicted as a colour spectrum ranging from blue over green and yellow to red. The vertical lines represent the excitation wavelengths (488nm, 543nm and 633nm). The dashed lines symbolize the emission curves of the selected fluorochromes, in this case FITC, TRITC and Cy5, and are intended to help to set the detection bandwidths (grey rectangles below the measuring scale of the spectrum). There are also the selection boxes of the single detectors below the spectrum. The sliders used to adjust the intensity of the excitation wavelength are positioned above the spectrum. On the right side of the dialog there are the selection boxes with the so-called *instrument parameter settings*, which have been preset by the factory (red "L") or by the user (blue "U").

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which consists of two independent galvanometer-driven mirror systems, makes it possible to freely rotate the scan field and to achieve a high image recording rate. Via an optical output the signal can be transmitted to external devices, such as a Raman spectrometer. The TCS SP2 is designed for simultaneous image recording in up to 8 detection channels. As an option the bit depth of each detection channel can be set to 8 or 12 bit. A SCSI interface enables fast data transfer to the PC.

In summary, the Leica SP spectrophotometer detection system is a revolutionary new fluorescence detection system that has significant practical advantages and yet is less complex and easier to use than conventional filter based systems.

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Confocal Spectrophotometry (continued)

by U. Tauer and O. Hils

nal for DAPI would be picked up also in the area of the FITC detection band. Other examples are combinations of the fluorochrome FITC/TRITC or Cy3/Cy5, shown further below as an example.

It is therefore preferable under such conditions to perform the individual steps in a Sequential Scan. For, in sequential scanning mode only one laser line causes excitation and detection occurs in only one detection range which results in a considerable reduction of crosstalk. Within a limited scope, the efficiency of the detection can also be increased because a wider spectral area can be chosen for detection. However, it should also be noted that fluorochromes can also be non-specifically excited by shorter wavelengths, which can lead once again to a faulty interpretation. If, for example, the detection of FITC (excitation at 488 nm) in the long wavelength area is set too large, the fluorescence of non-specifically excited TRITC molecules in the "FITC channel" can be detected as well, even when the adequate excitation wavelength of TRITC are actually the laser lines 543 nm or 568 nm (and not 488 nm).

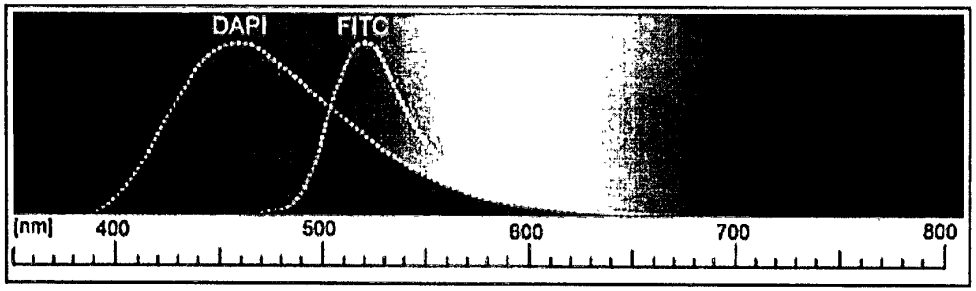

Fig. 4: The emissions spectra of DAPI and FITC (literature values) overlap over a wide range of about 480 to 600 nm.

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SCIENTIFIC AND TECHNICAL INFORMATION
Special issue "Confocal Microscopy", CDR 4, pp. 28–44, October 2000

Software in confocal microscopy

by F. Olschewski, Leica Microsystems Heidelberg GmbH

Introduction

Optical microscopy and spectroscopy are measuring processes of decisive importance in many fields of medicine and biology. Many of the measuring devices used here combine traditional microscopes with modern computer technology. Examples of this are the confocal laser scanning microscope (CLSM) and the multiphoton microscope (MPM) which allow insight into the three-dimensional structure of small, living samples.

This paper illustrates the principle and applications of confocal microscopy and their dependence on software and computer technology, using the laser scanning microscopes made by Leica and the associated software as examples.

Products, principles and hidden software in imaging

Leica has developed different microscope systems for various applications, the differences being in realisation, task formulation and flexibility. The product range includes

- the Leica ICM 1000 (industrial confocal microscope), a confocal reflection microscope for accurate measurement of surfaces;
- the Leica TCS SP2 (spectral confocal microscope), a confocal fluorescence microscope with spectrally freely adjustable detector;
- the Leica TCS MP 2 (multiphoton microscope);

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Software in confocal microscopy (continued)

by F. Olschewski

- the predecessors of these systems, the TCS NT (confocal microscope), TCS SP (spectral confocal microscope), and TCS MP (multiphoton system).

The confocal microscopes create a three-dimensional image by means of special pinhole optics. Figure 1 outlines the principle involved. A pinhole, inserted as an additional aperture in the beam path, reduces optical imaging characteristics to a small sample volume at the focal plane of the microscope. Arrangements of this type eliminate non-focal portions of the image and achieve a more compact point response (point spread function) and higher image fidelity in comparison with conventional methods of light microscopy. The resulting image quality has higher resolution (Rayleigh criterion). A similar effect can be achieved in a multiphoton system using a pulsed laser and without the use of any pinholes at all. In these systems, multiquantum effects create a similar imaging function which also causes greater depth of tissue penetration and less harmful transmission of the radiation load to the tissue. For example a detailed description of these technologies can be found in Pawley [7].

In both cases, reduction of the detection volume parallel to the optical (z) axis causes real resolution along this axis. This characteristic is the essential innovation: it is known as ‚optical sectioning', and is the fundamental basis for three-dimensional measurement of complex structures in the field of microscopy[1]. These characteristics cannot be achieved by the conventional procedures of light microscopy. They can be approximated after using complex image restoration algorithms (deconvolution), but these go hand in hand with very long processing times.

"Optical sectioning" is just as important in molecular and cell biology as the innumerable methods of computer-based to-

[1] In addition, resolution within the focal plane is slightly increased in comparison with standard procedures.

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Software in confocal microscopy (continued)

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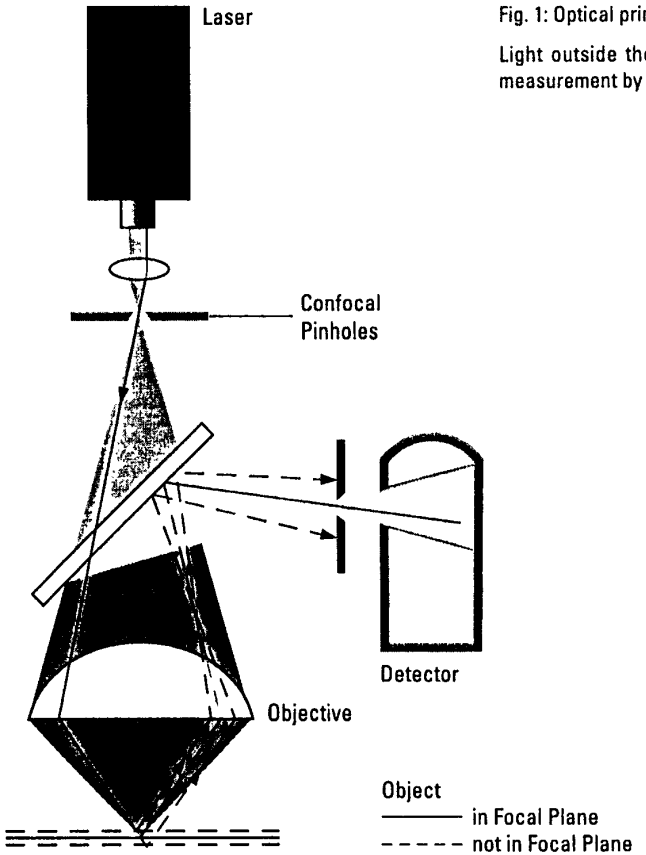

Fig. 1: Optical principle of confocal microscopy.

Light outside the focal plane is excluded from the measurement by an additional aperture (pinhole).

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Software in confocal microscopy (continued)

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mography in medicine. With fluorescence operation, it is possible to look into the living sample without the necessity of physically cutting it into slices.

Software is already being used for image generation with all these point-based recording processes. Most users are unaware of this, since this part of the software is relatively well hidden and is an expected component. However, the recording described above occurs only in a very small detection volume which can also be described, more or less correctly, as a point. In order to obtain the image of a sample, it is necessary to scan a grid of measurement points. This is undertaken sequentially by means of temporal deflection of the light, with the detection volume moving through the sample. In addition to all the mechanical-optical mechanisms which need to be used to deflect the beam, this is primarily a software-compatible task of regulation and control.

All of the more recent Leica systems are equipped with a scanner which can be moved very fast for beam deflection (K-scanner), and with hybrid control electronics. In addition to analogue switching circuits, the control electronics also contain a microcontroller and field programmable gate arrays (FPGAs). The advantages of these individual components can be summarised as follows:

- Analogue switching circuits take over specific processes for which time is an extremely critical factor.

- Microcontrollers are extremely flexible processors with a large number of input and output options that are designed for tasks such as decision-making and control. For this reason, they are extremely suitable for coordination, control and diagnosis within the system.

- FPGAs take over signal-processing tasks. An FPGA is basically a chip containing a large number of digital gates. The configuration of these gates can be

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altered. The configuration itself can take up all types of digital circuits and is fundamentally a part of software which is merely loaded onto the chip. In this manner, every typical signal processing task[2] can be achieved directly in the FPGA, with the advantage that they operate with the full clock-pulse rate of a specific circuit. This characteristic, which is typical for FPGAs, is not found in other processors, microcontrollers or even digital signal processors.

The overall system achieves its performance as a result of intelligent linking of the individual components. It is easy to solve a required measurement and control task in this case if the required intelligent mechanisms are close to the actual process and are fast enough to keep up with that process. This has been successfully achieved with the control electronics of the new TCS SP2 technology, which solves tasks such as beam positioning and region-dependent illumination with precise, rapid timing.

General tasks of the application software

A confocal microscope has to carry out various tasks during and after an experiment. In addition to optical image generation, electronic signal conditioning, monitoring the individual components and data acquisition, there are also computer-based tasks, such as data storage and retrieval, image analysis, image processing and visualisation.

Application software is present on the control computer for these tasks. These tasks have been resolved uniformly for the whole product range (TCS NT,SP, MP, SPII, MPII, ICM 1000) with the recent introduction of Leica Confocal Software (LCS). Leica LCS has been specifically designed for the requirements of 3D imaging and higher-dimensional microscopy and offers the user a stan-

[2] The interested reader is referred to [4] for information on the realisation of some typical processing tasks.

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dard and ergonomic graphical user interface and compatibility for all products.

A schematic overview of the multi-tier architecture of Leica LCS can be found in Figure 2. All the application-specific software features have been integrated in a global application logic with a COM interface. The actual functions are to be found in small, server-like, enclosed structures, which cover a single task area in a highly specialised fashion. For example, the drivers for specific hardware components (scanner, desk) are combined in one of these groups. More complex tasks, such as recording a volume, can be found in a different group. When it comes to concrete operation, the more complex group resorts to the services of the simpler group. This modular form of construction, from the detail to the abstract function, allows applications to be realised independent of hardware. The software architecture allows by means of exchanging individual components the exchange of individual system components right up to the support of new types of microscope. Implementation is in C/C++ [8] according to the rules of object-oriented system development [6, 1].

Many of the software features have been optimised for 3D imaging. Navigation through the three-dimensional data record, for example, is simplified by means of visualisation ("Series Scan Overview", cf. Figure 3.). An overview shows the breakdown of the 3D space into the individual levels to be recorded, as well as the start and end positions during recording. The geometry of the sample and the internal status of the unit can thus be read at any time. This is not essential for operation but does increase the ergonomics of the system considerably.

There is also support for recording higher-dimensional images. For example it is necessary in an evolutionary analysis to record several volumes over a period of time and to visualise these afterwards.

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Software in confocal microscopy (continued)

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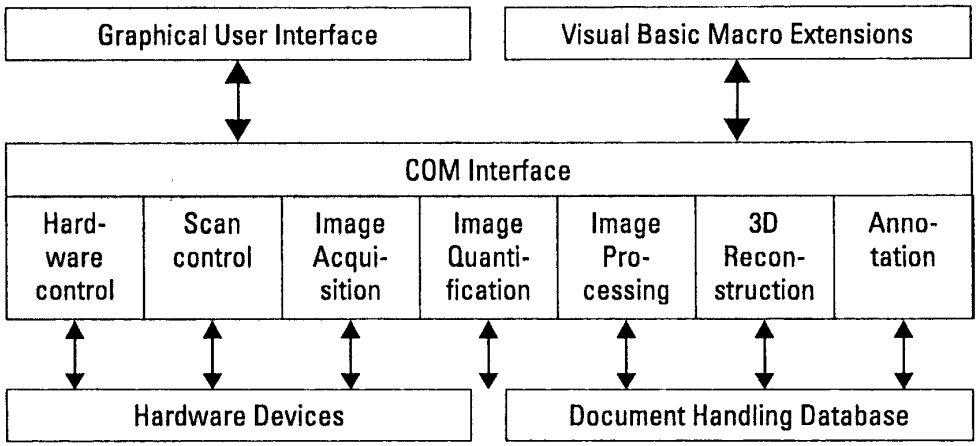

Fig. 2: Overview of Leica LCS software architecture.

Various servers, specialised for individual tasks (3D, imaging, instrument control), are combined in a common application logic to form a single architecture and made available to the macro package and other applications via an automation interface (COM).

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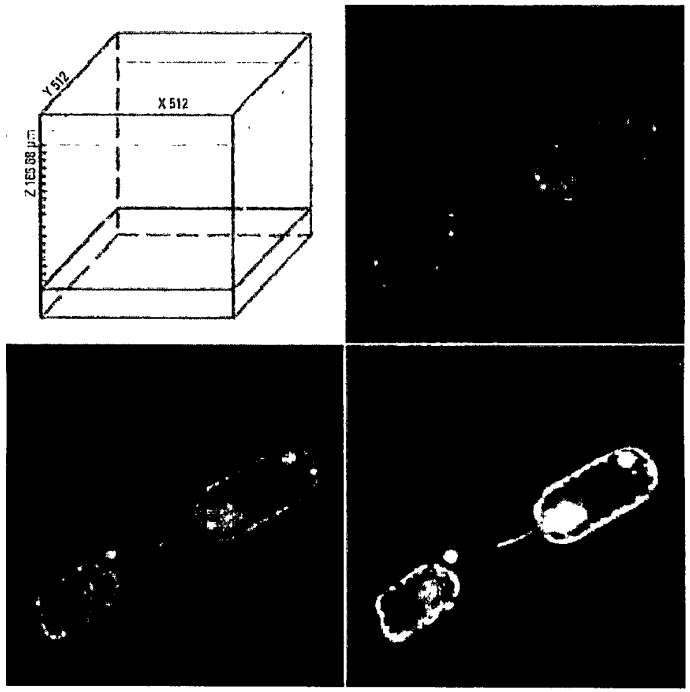

Fig. 3: From sections to stereo representations

The sample is a planctonic marine diatom (Ditylum brightwellii).
a) Overview of the recording geometry.
b) Section of the volume at the yellow position in (a).
c) Transparent projection of the total volume.
d) Stereo transparent projection.

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Special object-oriented software structures have been created in order to achieve tasks such as these in a simple manner, with the ability to record and process data records of any size. This solution is well matched to the problem. In addition this approach also includes efficient memory management adapted to the large amounts of data to be expected. This technology makes it possible to carry out complex analysis functions easily with one click of a button.

Because of the varied nature of the applications, a Visual Basic™ macro language has also been integrated in the software. This allows access to the internal structures of LCS via an object-oriented interface and the option of adapting it to any conceivable application. For this purpose, the individual LCS software components – from hardware control to visualisation – are equipped with a special interface which is presented as a Visual Basic™ object hierarchy. A spectrometer (e.g. Leica TCS SP2) exists in this hierarchy as a spectrophotometer object and passes on control commands via the application logic to the hardware. Other objects are the imagetool object, which makes image processing functions available, and the imagetool.renderer object, which specialises in 3D visualisation.

Fluorescent stains

The majority of confocal applications are found in the field of biology. Since it is a non-destructive, non-invasive measurement method, it is highly suitable for recording living cells at high resolution. The use of fluorescent stains is important since biochemical and molecular biological agents can be used to stain specifically almost any component within a cell. In this context, methods, such as FISH (fluorescence in situ hybridisation) and dyes, such as GFP (green fluorescent protein) should be mentioned in particular. A series of conditions must be borne in mind for the optimum recording of stains of this type. The

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laser lines which are usable for light exposure and the adjustment of the spectrophotometer or selection of the filters must be adapted to the stains used. LCS supports this configuration by means of appropriate management of defaults and by pre-setting for frequently used dye combinations.

After measurement, images or image stacks are obtained for each measurement channel and must be superimposed again by the software to yield a true-colour image. These images have a few interesting characteristics, since the data separation which is often expected does not occur for a variety of reasons. Instead, mixed data are observed in the individual images. The detailed reasons for this are as follows:

1. Some structures within the sample bind to several dyes simultaneously. This is known as co-localisation.

2. With filter-based systems, it is not always possible to perform optimum optical separation of the signals to be observed. Crosstalk is observed which can, in theory, be removed again. But appropriate adjustment of the spectrophotometer of the TCS SP2 can be used to eliminate these effects at the source.

Effects of this type may be analysed using the Leica LCS Multicolor Package. J. Davoust introduced the multicolour analysis procedure and the term cytofluorogram into the field of confocal microscopy [3]. This approach combines multivariate analyses of the cytofluorometry with microscopy and is ideally suited for the analysis of co-localisations within the sample. The cytofluorogram is a discrete estimation of the joint probability function of the recorded intensities $\vec{I}$. For this purpose, the relative frequency $h(\vec{I})$ is plotted in colour-coded form at the $\vec{I}$ level in order to obtain an impression of the distribution function. The stain concentrations are converted to intensity in the microscope. This is approximately a linear transformation and pre-

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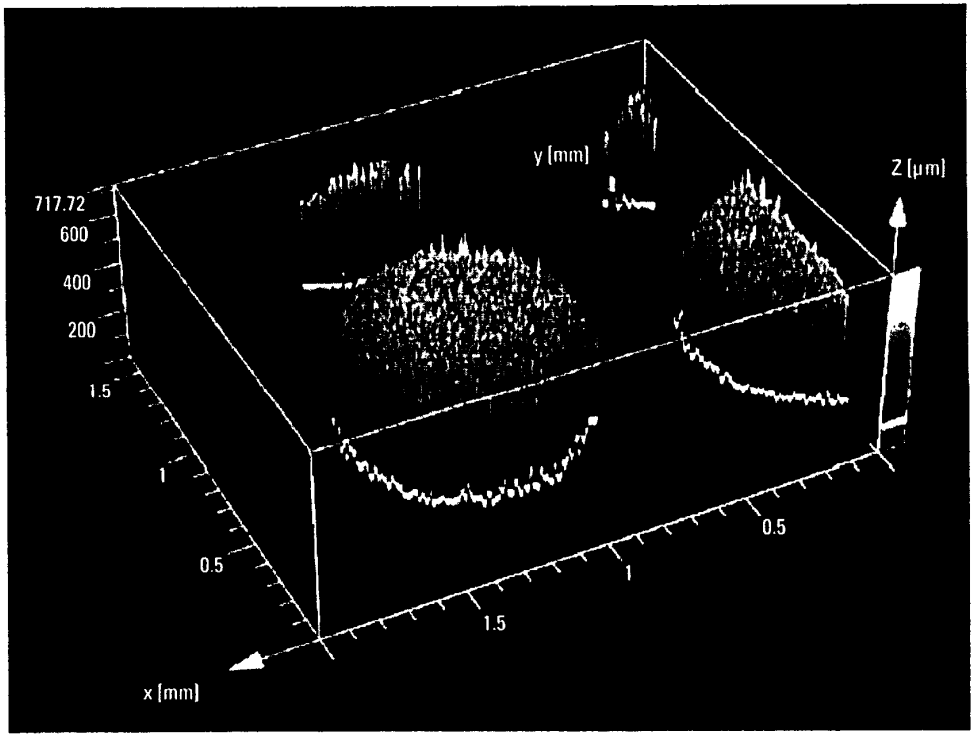

Fig. 4: Printed Circuit Board (PCB)

Surface representation of a contour image of the PCB. Because of the high dynamics caused by the major differences in height between the PCB and the solder, a special non-true colour representation was used to show the detail of the PCB.

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serves the geometry. For this reason, crosstalk and co-localisations are detected as straight lines in the cytofluorogram.

LCS supports these tasks by individual calculations, specific representations of the cytofluorogram and manual segmentation processes. Realisation based on OpenGL means that visualisation of three-dimensional cytofluorograms is also possible.

Visualisations

Confocal data records consist of individual images which have to be combined to form a single volume, either by the software or the user. Although the individual images contain more details than conventional light microscopy images, generally these cannot be utilised directly by the user. Analysis of three-dimensional structures on the basis of sectional images alone is difficult, and requires high levels of expertise and skills of three-dimensional imagination. Visualisation techniques simplify this task since they (re)construct three-dimensional views of the sample. They help the user to obtain a spatial impression of the sample. Although all volume visualisation techniques are very computationally intensive, the LCS 3D package presents an extremely fast solution without compromising image quality.

Reflection measurements are chiefly used to characterise surfaces. Since reflection also plays a part in our everyday lives, visualisation mechanisms have become established in graphics standards, such as OpenGL. The principle is relatively simple and utilises the effect of concealment and opacity. The surface is modelled as a polygon model and sent via OpenGL to the graphics card where real-time processing takes place by means of the graphics chip. This mechanism is used by LCS after the surface has been determined through segmentation (cf. Figure 5).

Fluorescing objects possess more problematic characteristics: they are transpar-

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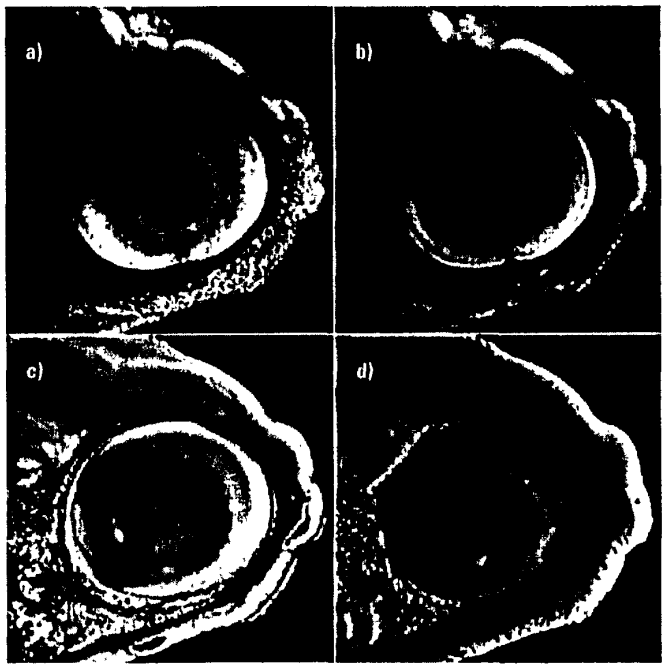

Fig. 5: Overview of the different projection methods

The sample is a zebra fish larva. The projection looks through the eye from the inside. The methods (from top left to bottom right) are:
a) Maximum projection,
b) Mean value projection,
c) Transparent projection,
d) SFP projection.

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ent and suitable segmentations can be obtained only with difficulty.

For this reason, volume-based processes are used for visualisation in LCS 3D. These algorithms project the three-dimensional volume on to the two-dimensional screen. All the recorded data must be run through for each angle of view and superimposed on the screen in accordance with the visualisation specification. The individual projection methods are as follows (cf. Figure 5):

- Maximum projection shows the brightest point on the line of sight. The resulting image shows the most conspicuous structures within the volume. However, it is not a realistic three-dimensional view because the object looks the same from the front and the back.

- Average projection calculates the mean intensity on the line of sight and, in terms of quality, can be compared to maximum projection with poor dynamics.

- Transparent projection models the transparency of the material and the decrease in light along the line of sight. Genuine three-dimensional representations are thus obtained since all the different angles of view generate different images.

- SFP projection (simulated fluorescence process algorithm) is the most realistic for fluorescence because the fluorescent effect is simulated in the computer [9]. The process permits different directions of illumination and a virtual shadow of the object.

The individual projection processes can be combined as required with animations and/or stereo views. For both of these purposes, the projections are calculated for different angles of view. In the case of animations, the angles of view are selected such that a virtual trajectory is swung in around the object. Stereo combines two slightly displaced angles of view (interocular distance

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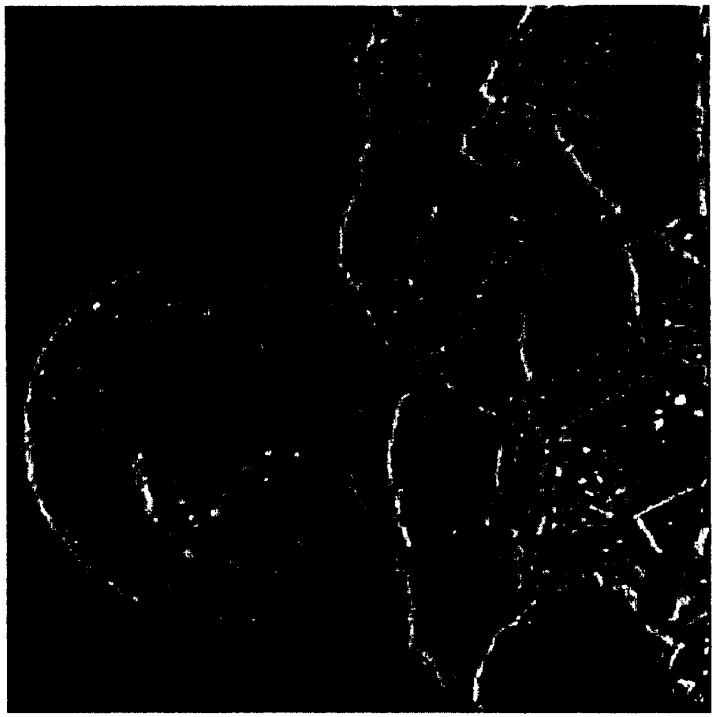

Fig. 6: Stereo-SFP

Representation of a polymer as a stereo SFP projection (red/green anaglyph).

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approx. 6°) of the projection and blends the images into a red-green representation. When viewed with red/green spectacles, this results in genuine three-dimensional perception.

Conclusion

It is impossible to realise confocal or multiphoton microscopes without using software. Application software, in particular, is essential. This applies both to control of the device itself and, in particular, to the analysis and presentation of the recorded data material. With the introduction of Leica Confocal Software (LCS), Leica has created a common control and evaluation platform for all confocal products.

Acknowledgement

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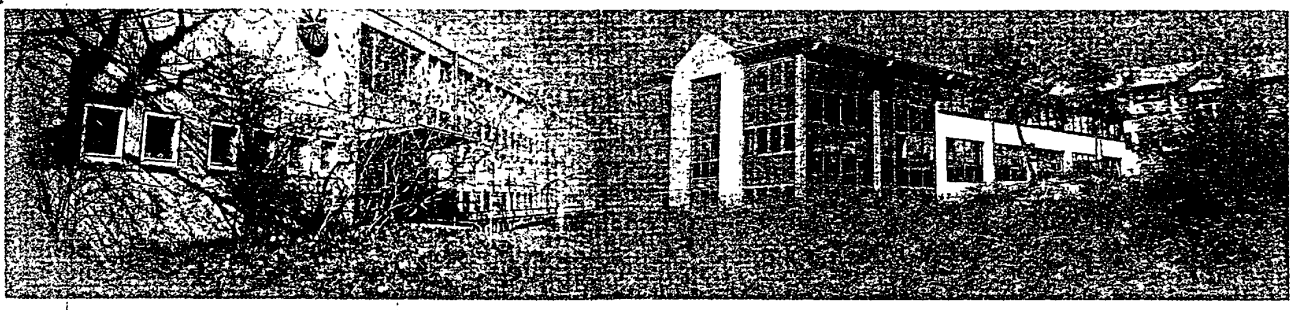

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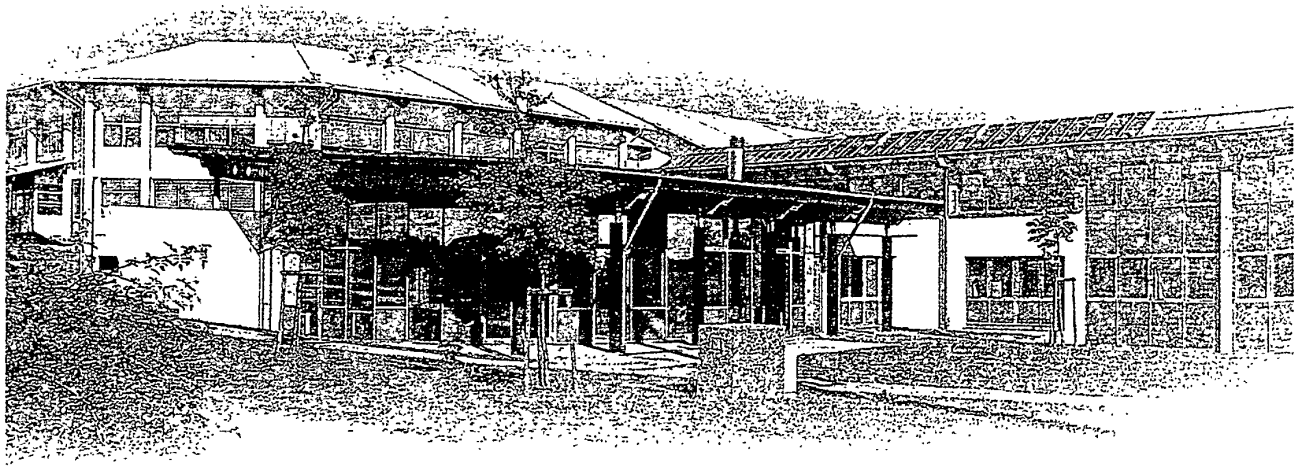
Kompetenz in Mikrosystemtechnik
Competence in Microsystems

Innovationsfreudige Unternehmen vertrauen dem HSG-IMIT schon seit 1988 ihre Produktideen an. Der Anteil des Industriegeschäfts am Forschungs- und Entwicklungsvolumen verdoppelt sich seit 1996 jährlich. Für diesen erfolgreichen Weg gibt es Gründe: Konzentration auf Kernkompetenzen, hervorragende Ausstattung, Routine in der Realisierung von Innovationen, Beobachtung der Markttrends, enger Kontakt zur Industrie vor Ort und weltweit, prozessorientiertes Managementsystem nach ISO 9001:2000, letztendlich ein kundenorientiertes Führungssystem.
Den wissenschaftlichen Nährboden für eine hohe Innovationskraft schafft das HSG-IMIT durch eine enge Kooperation mit den Universitäten Stuttgart und Freiburg in Forschung, Ausbildung und Anwendungsentwicklung.
Die Ernennung zum Liquid Handling Kompetenz-Center der Europäischen Kommission unterstreicht den hohen Stellenwert des HSG-IMIT – nicht nur als regionales sondern auch als internationales Mitglied im „Innovations-Cluster" der Forschungs- und Dienstleistungseinrichtungen.

Die Stärken des HSG-IMIT liegen in der Sensorik, Mikrofluidik, Informationstechnik und definierten Herstellungsprozessen. Innerhalb der Fachgebiete liegt der Schwerpunkt auf wachstumsstarken, vielfältig einsetzbaren Produktbereichen, besonders Inertial- und Durchflusssensoren sowie Mikroschalter, Mikrodosierung und -pneumatik. Kurz: Wo Objekte und Materie bewegt werden und diese Bewegungen äußerst effizient, präzise, zuverlässig und kostengünstig auf kleinstem Raum gemessen und gesteuert werden müssen, bietet das HSG-IMIT Lösungen unter Einsatz der Mikrosystemtechnik an.
Das Institut greift Ideen auf und generiert Projekte aus der eigenen wissenschaftlichen Arbeit. Die Teams am HSG-IMIT prüfen die Machbarkeit, entwickeln und bauen Prototypen und organisieren schließlich die Serienfertigung für bzw. mit Kunden. Die Erfahrung und die Methode, Bewährtes mit Neuem zu verbinden, führt zu einem kurzen „Time-to-market".

Prof. Dr. Hermann Sandmaier
Leiter des HSG-IMIT.

Prof. Dr. Hermann Sandmaier
Director of the HSG-IMIT.

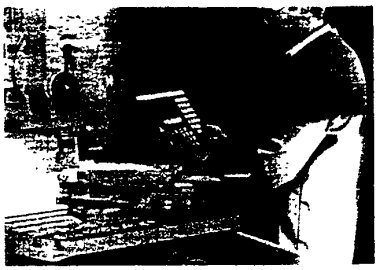


Companies appreciative of innovation have been entrusting HSG-IMIT since 1988 with their product ideas. Beginning in 1996 the volume of industry business in research and development has doubled every year.
This success is not without its reasons which are: concentration on core competencies, excellent facilities, experience in the realization of innovations, observation of market trends, close contact to local and worldwide industry, a process-oriented management system according to ISO 9001:2000 and finally customer-oriented management.
The scientific breeding ground for high-level innovation personnel is provided by HSG-IMIT through cooperation with the Universities of Stuttgart and Freiburg in research, training and application development.
Being named as Liquid Handling Competence Centre for the European Commission underlines the significance of the HSG-IMIT – not only as regional but also as international member in the „Innovation-Cluster" of the research and development facilities.

The strengths of the HSG-IMIT are the areas of sensors, microfluidics, information technology and defined production processes. Within the specialized areas, the concentration is on fast-growing, versatile product areas, particularly inertial sensors, flow sensors and microswitches, micro dosage and pneumatics. In other words: HSG-IMIT offers solutions employing microsystem technology wherever objects and matter are being moved and this movement must be controlled and measured with extreme efficiency, precision, reliability, in minuscule areas and at a minimum of cost.
The institute picks up ideas from its own scientific work and generates projects therefrom. HSG-IMIT teams test feasibility, develop and build prototypes and finally organize series production for and with clients. The experience and the method of bringing that which is proven together with that which is new leads to a short „time to market".

Beweis für den internationalen Stellenwert: Das HSG-IMIT ist Kompetenz-Center der Europäischen Kommission.

Evidence of its international significance: The HSG-IMIT is EU Competence Centre.



Konsequent marktorientiert
Persistently market-oriented

Der Markt fragt nach neuen Technologien mit „eingebauten" Wettbewerbsvorteilen und Wachstumschancen. Das HSG-IMIT nutzt diese Potenziale und konzentriert sich auf definierte Zielmärkte:

- Automotive
- Life Sciences
- Produktions- und Automatisierungstechnik.

Das HSG-IMIT unterstützt Unternehmen mit seinem klar strukturierten Dienstleistungsangebot und der nötigen Infrastruktur zur Konstruktion und Herstellung mikrosystemtechnischer und informationstechnischer Komponenten und Systeme für diese Zielmärkte. Das Dienstleistungsangebot richtet sich an Unternehmen im In- und Ausland, die die Vorteile neuer Technologien nutzen und Risiken im Vorfeld der Produktion verringern wollen.

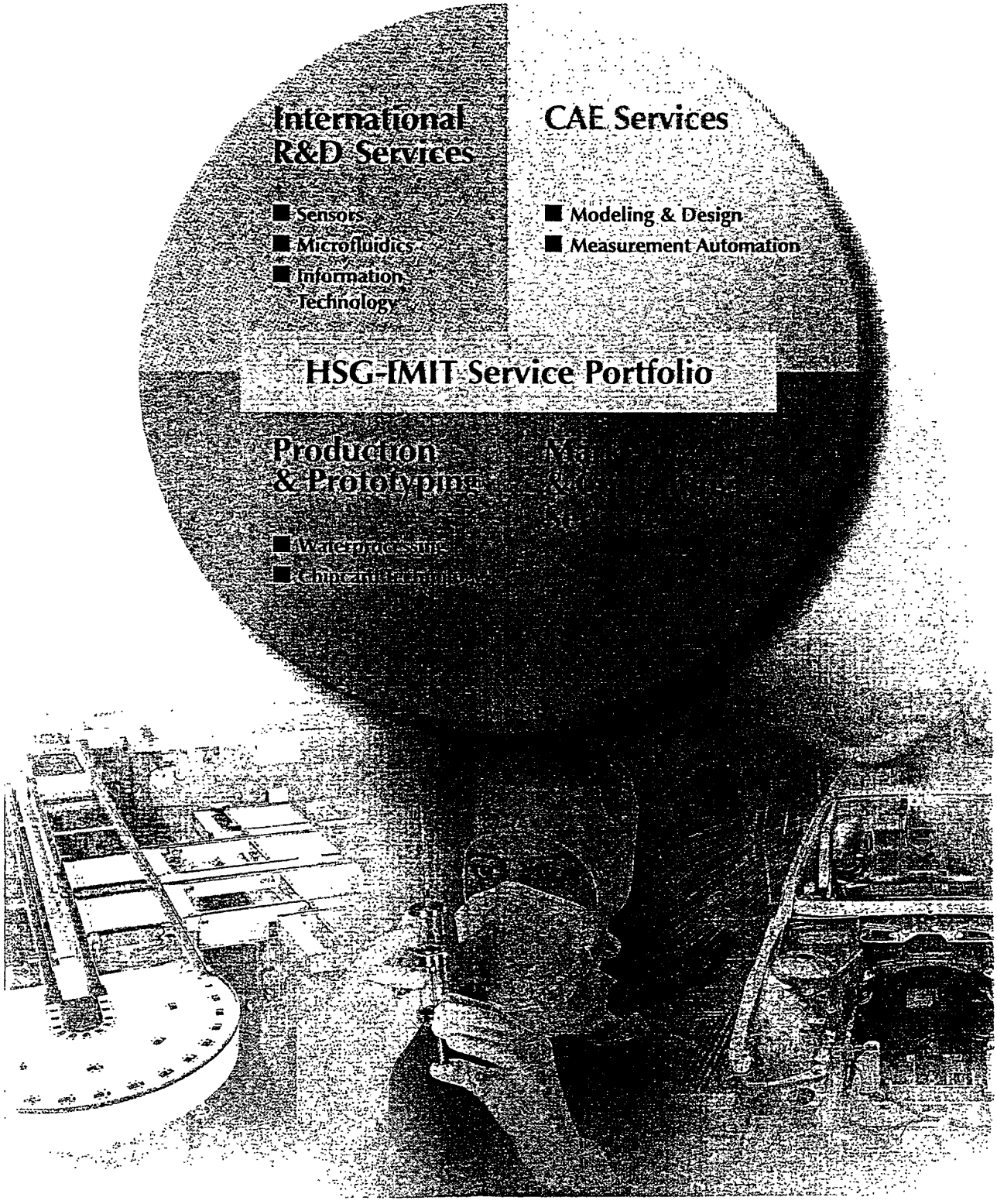
Entwicklungsaufträge führt das Institut direkt und vertraulich bis zur Serienreife aus. Daneben nutzen industrielle Auftraggeber und Partner des HSG-IMIT die Möglichkeiten der öffentlich geförderten Verbundforschung. In enger Kooperation schaffen mehrere Firmen und das Institut gemeinsam die Grundlagen für erfolgreiche Produkte der Zukunft. In allen Fällen lautet die Dienstleistungsphilosophie: Von der Idee zur Produktion – alles aus einer Hand.

The market calls for new technologies with „built-in" competitive advantages as well as possibilities for growth. HSG-IMIT is using this potential and is concentrating on specific target markets:

- *Automotive*
- *Life sciences*
- *Production and automation technology*

With its clearly structured offer of services and the necessary infrastructure for the construction and production of microsystem and information technical components and systems, the HSG-IMIT supports companies in these target markets. The range of services available is directed to domestic and foreign companies interested in using the advantages offered by the new technologies and in reducing risk involved in the preliminary stages of production.

Development contracts are confidentially carried out by the institute through to series production. In addition, industrial contractors and partners of HSG-IMIT use the possibilities offered by the officially sponsored joint research. In close cooperation several companies and the institute are creating the basis for successful future products. In all of the applications the service philosophy is: from the idea to production – one source for all.

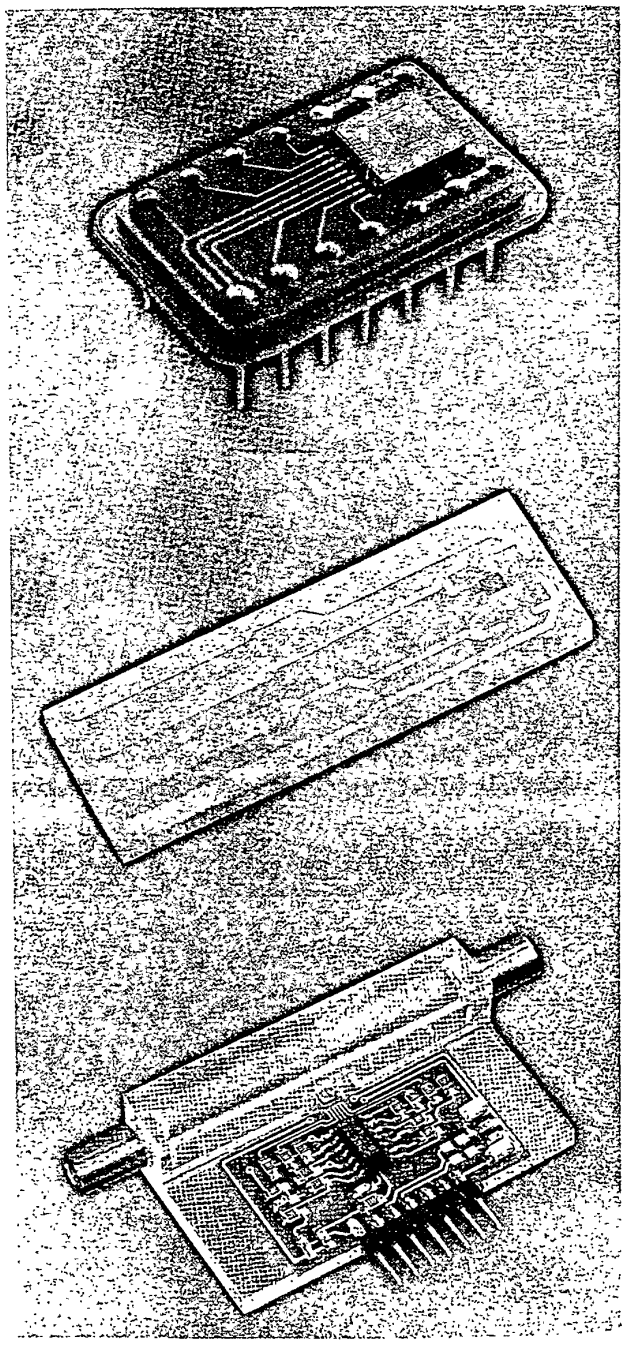

International R&D Services
Sensors
Microfluidics
Information Technology
CAE Services
Modeling & Design
Measurement Automation
HSG-IMIT Service Portfolio
Production & Prototyping

International
Research & Development Services

Sensors

Mikrotechnische Sensoren gelten als die Nervenenden der Elektronik. Sie erhalten ein immer feineres Gespür für Bewegungen, Strömungen, Temperaturen und Druck. Wo höchste Präzision in der Messung auf kleinstem Raum gefordert ist, finden diese Sensoren ihren Platz. Das HSG-IMIT entwickelt Inertial- und Strömungssensoren sowie Mikroschalter und realisiert konkrete industrielle Anwendungen.

Micro sensors function as the nerve endings in an electronic system. Their ability to sense movement, flow, temperature and pressure is being constantly improved. Wherever high measurement precision in minute areas is required, these sensors are the fitting choice. The HSG-IMIT develops inertial sensors, flow sensors, micro switches and realizes practical industrial applications.



In der Sensorik, Mikrofluidik, Informationstechnik und in speziellen Mikrotechnologien zählt das HSG-IMIT international zu den führenden Entwicklungsdienstleistern. Lösungen für die Biotechnologie, Analytik, Pneumatik und die Informations-Ergonomie am PC erzielen bereits Erfolge auf dem Markt. Das Institut generiert Innovationen von der Idee bis zum fertigen Produkt und organisiert die Serienfertigung. Kleine und mittelgroße Unternehmen erfahren volle Unterstützung durch Know-how-Transfer, Service und Beratung, wenn sie die Schlüsseltechnologie Mikrosystemtechnik nutzen wollen.

In microfluidics, sensors and information technologies as well as in other special micro technologies, HSG-IMIT is among the international leaders as development provider. Solutions for biotechnology, analytics, pneumatics and information ergonomics for PCs have already achieved success on the market. The institute generates innovations, seeing them through from their conception to their realization as finished product. Extensive support is available to smaller companies in the form of know-how-transfer, service and consultation should they wish to benefit from the advantages afforded by microsystem technology.

Inertial Sensors

www.hsg-imit.de

Drehratensensor DAVED® erfaßt Bewegungen ab 0,05°/s.

DAVED® angular rate sensor with a measuring accuracy of 0.05°/s.

Inertialsensoren messen Beschleunigung, Drehung im Raum und Neigung von frei beweglichen Objekten. Der Drehratensensor DAVED® z. B. misst sogar Drehbewegungen, die so langsam sind wie die Minutenzeiger einer Uhr. In Verbindung mit der Auswerteelektronik lässt sich DAVED® spezifischen Anwendungen anpassen: Navigationsysteme (auch mit GPS kombiniert), Airbag-Steuerung, Stabilisierungssysteme etc.

Inertial sensors measure acceleration, angular rate and inclination of moving objects. The DAVED® angular rate sensor for example measures even rotational movements as slow as the minute hand on a watch. Combined with the evaluation electronics, the DAVED® can be used for various applications: navigation systems (also in combination with GPS), airbag control, stabilizing systems etc.

Micro Switches

www.hsg-imit.de

Membranschalter, 1,6 x 2 mm groß.

Membrane switches, 1,6 x 2 mm.

Mikroschalter bieten eine zuverlässige Schaltfunktion auch unter rauhen Umgebungsbedingungen. Ihre Silizium-Membran – sie stellt in einem geschlossenen Hohlraum den Kontakt her – ist staubdicht und langzeitstabil. Innovative User-Maschinen-Interfaces von Tastaturen bis zu industriellen Sicherheitschaltern werden möglich.

Micro switches offer a reliable switching function even under severe environmental conditions. Their silicon membrane which produces the contact in a closed hollow chamber is dust-tight and remains stable over a long period of time. Innovative user-machine-interfaces are available for various uses including keyboards and industrial safety switches.

Flow Sensors

www.hsg-imit.de

Thermischer Strömungssensor für kleinste Volumenströme.

Thermal flow sensor for minute volume flows.

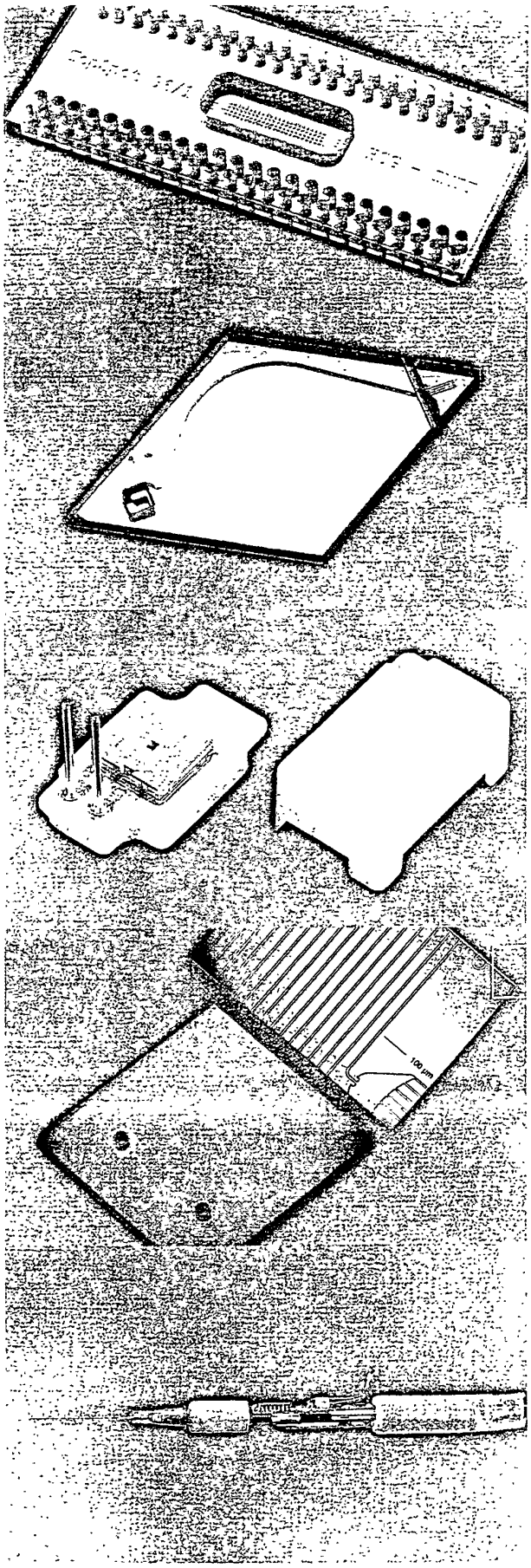
Wo Gase und Flüssigkeiten strömen, stellt sich die Frage nach Menge und Geschwindigkeit. Der Strömungssensor erfasst bei Flüssigkeiten schon kleinste Mengen, wenige Tropfen pro Stunde. Das mikrotechnische System nutzt thermische Effekte. Einsatzgebiete sind Kfz-Technik, Pneumatik und Anlagenbau, Bioanalytik und Medizintechnik.

Wherever gases and liquids flow, questions concerning volume and rate thereof arise. The flow sensor senses minute amounts, a few drops per hour. The micro technical system employs thermal effects. Fields of application are motor vehicle engineering, pneumatics and chemical plants, bioanalytics and medicine.

Microfluidics

In Wachstumsbranchen wie der Biotechnologie, aber auch in der Medizintechnik steigt der Bedarf an wirtschaftlichen Systemen, die kleinste Flüssigkeits- und Gasmengen präzise und effizient transportieren, dosieren, schalten und messen. Know-how in der Mikrofluidik ist die Voraussetzung für die Entwicklung dieser Systeme. Das HSG-IMIT verfügt im Haus und in einem Kompetenz-Netzwerk mit der Uni Freiburg über einzigartige Fähigkeiten zur schnellen Entwicklung serienreifer industrieller Anwendungen der Mikrofluidik.

In rapidly expanding industries such as biotechnology and medicine the need for cost-effective systems capable of transporting, dosing, switching and measuring minute volumes of fluid and gas efficiently and precisely is continually increasing. Prerequisite for the development of such a system is knowledge and ability in the field of microfluidics. The HSG-IMIT is – in its own premises as well as through a competence network together with the University of Freiburg – in charge of unique skills to quickly develop microfluidic industrial applications for series production.



Microarrays

www.hsg-imit.de

Auf 7 mm² erzeugen 96 Düsen Tropfen-Arrays für Biochips.

In an area of 7 mm², 96 nozzles produce droplet-arrays for biochips.

Die am HSG-IMIT entwickelte TopSpot Methode ist das erste Spotting-Verfahren zur Serienherstellung von Biochips und kann bis zu 1000 unterschiedliche Analysesubstanzen auf einen Biochip drucken. Das entwickelte Modul bringt die Substanzen als Nanoliter-Tropfen im Raster von wenigen hundert Mikrometern auf den Träger und reproduziert diese Arrays in hoher Präzision.

The TopSpot technique developed by HSG-IMIT is the first spotting procedure for serial manufacturing of biochips. It is capable of placing up to 1000 different analyzing substances on a chip. The module developed applies the substances as nanoliter droplets in a pattern of a few hundred micrometers to the chip and reproduces these arrays with high precision.

Pipettes & Dispensers

www.hsg-imit.de

Nanojet Dispenser für exakte Dosierung ab 5 nl.

Nanojet dispenser for exact dosage starting at 5 nl.

Mit der Nanojet-Technologie lassen sich flüssige Medien schon ab einem Volumen von fünf Nanolitern exakt dosieren. Das mikrotechnische Dosierverfahren reduziert Einflüsse von Medieneigenschaften und Temperatur. Pipetten und Dispenser erreichen damit eine neue Dimension der Präzision. Labore sparen Analysesubstanzen bei gleichzeitig verbesserter Dosierpräzision.

Nanojet technology enables the exact dosing of fluids starting at a minute volume of five nanoliters. The micro technical dosing procedure reduces the influence of medium characteristics and temperature. With this development, pipettes and dispensers have reached a new dimension in precision. In addition laboratories can save on analyzing substances through the improved efficiency of the dosage precision.

Microvalves

www.hsg-imit.de

Mikroventile schalten bis 16 bar Druck und arbeiten bei Temperaturen von -50° C bis +200° C.

Microvalves can switch up to 16 bar pressure and function between - 50° C and + 200° C.

MegaMic® eröffnet der Pneumatik neue Dimensionen. Das vom HSG-IMIT in Kooperation mit Hoerbiger-Origa entwickelte Mikroventil arbeitet schneller, energiesparender und robuster als herkömmliche Komponenten. Es ist verschleißfrei und temperaturunempfindlich. In Feldbus-gesteuerten Anlagen lässt sich das intelligente Bauteil leistungslos ansteuern.
Das Ventil schaltet bis 16 bar Druck – auch unter extremen Bedingungen.

MegaMic® widens the scope of pneumatics. Developed by HSG-IMIT in cooperation with Hoerbiger-Origa, this microvalve is more robust, more cost-efficient and functions quicker than its conventional counterpart. It is non-wearing and insensitive to temperature. In a field bus controlled unit, this intelligent component can be operated without power consumption. This valve switches up to 16 bar pressure – even under extreme conditions.

Fluidic Disposables

www.hsg-imit.de

Mikrotechnische Einwegsysteme für schnelle Analysen (Detailvergrößerung).

Microtechnological one-way system for fast analysis (enlargement of details).

Die Produktgruppe Fluidic Disposables entwickelt kostengünstige Einwegsysteme, die überwiegend in medizinischen und biochemischen Analysesystemen eingesetzt werden.
Dadurch lassen sich umfangreiche Reinigungsprozeduren herkömmlicher Analysegeräte vermeiden. Fluidic Disposables zum Beispiel ermöglichen schnelle und einfache Blut-Analysen.

The product group fluidic disposables develops cost-efficient one-way systems predominantly for implementation in medical and biochemical analysis systems. Extensive cleaning procedures associated with the use of conventional analyzing devices can thereby be avoided. Fluidic disposables enable for example the quick and simple analysis of blood.

Microdosage Systems

www.hsg-imit.de

Mikrodosierung wird mobil.

Microdosing becomes mobile.

Autonome, batteriebetriebene Mikrodosiersysteme realisiert das HSG-IMIT unter anderem für Einsätze in der Medizin. Sie geben geringste Flüssigkeitsmengen auf kleinstem Raum kontrolliert ab, zum Beispiel als implantierbares Medikamentendosiersystem. Bewährte Fluidelemente, Piezoaktoren und spezifische Elektronik sorgen für einen zuverlässigen und energiearmen Betrieb.

Medicine is one of various fields of application for the independent, battery powered microdosage systems realized by the HSG-IMIT. An example would be implantable drug-dosage systems where minimal size and capability of regulated dispensation are needed. Proven fluid elements, piezo actuators and specific electronics provide for reliable and energy-efficient function.

Information Technology

Die Informationstechnik des HSG-IMIT entwickelt Systemlösungen, damit kleinste Sensorsignale und Dateneinheiten über geeignete Kommunikationswege effizient weitergeleitet werden und nutzbare Informationen entstehen, die Entscheidungen auf der Verarbeitungsebene erst ermöglichen. Mit der Ansteuerung der Aktoren übernimmt die Informationstechnik auch die rückführende Kommunikation aus der System- in die unterste Prozessebene. Einsatzbereiche der integrativen Systemlösungen sind die Fabrikautomation, die Steuerung von Prozessanlagen, die Regelung autonomer, mobiler Systeme und spezielle Anwendungen auf den Märkten der Mikrosystemtechnik im Umfeld der vom HSG-IMIT entwickelten Produkte.

HSG-IMIT's information technology develops system solutions that enable even the slightest sensor signals and smallest data items to be efficiently relayed via suitable communication paths. This in turn makes the effective processing of information required for decision making at the highest system processing level possible. With the operation of the actors, the information technology also takes on the system's return communication at the lowest process level. Areas of application for the integrative system solutions are manufacturing automation, operation of processing units, control of autonomus, mobile systems and special applications in the microsystem technology markets in the areas of the HSG-IMIT developed products.

Informationstechnische Lösungen auf kleinstem Raum mit einem Minimum an Energieverbrauch sind eine Spezialität des HSG-IMIT. Optimierte Mess-, Steuer- und Regelalgorithmen ermöglichen hochintegrierte Bauteile, effiziente Firmware und autonome, intelligente Einheiten. Innovatives Energiemanagement sorgt für maximale Standzeiten der Systeme in mobilen Geräten.

Information technical solutions requiring a minimum of space and energy are one of HSG-IMIT's specialties. Optimized measurement and control algorithms enable high component integration, efficient firmware and independent smart units. Innovative energy management provides for maximum system service life in portable devices.

Controller

www.hsg-imit.de

Leiterplatten – Grundlage moderner Technologien.

Printed circuit boards – the basis of modern technology.

Signale und Daten müssen in komplexe Informationsstrukturen, Regelkreise, Datenbanken und Software-Umgebungen eingebracht werden. Ziel ist das optimale Zusammenspiel aller Komponenten. Dazu entwickelt die Informationstechnik des HSG-IMIT Systemlösungen auf der Basis von Standard-Programmiersprachen, effizienter Schnittstellen, bewährter Kommunikationstechnologien und Protokollen.

Signals and data must be imported into complex information structures, control loops, data banks and software environments. The object is the optimal interplay of all the components. To achieve this, HSG-IMIT develops system solutions based on standard programming languages, efficient interfaces, proven communication technology and protocols.

System Integration

www.hsg-imit.de

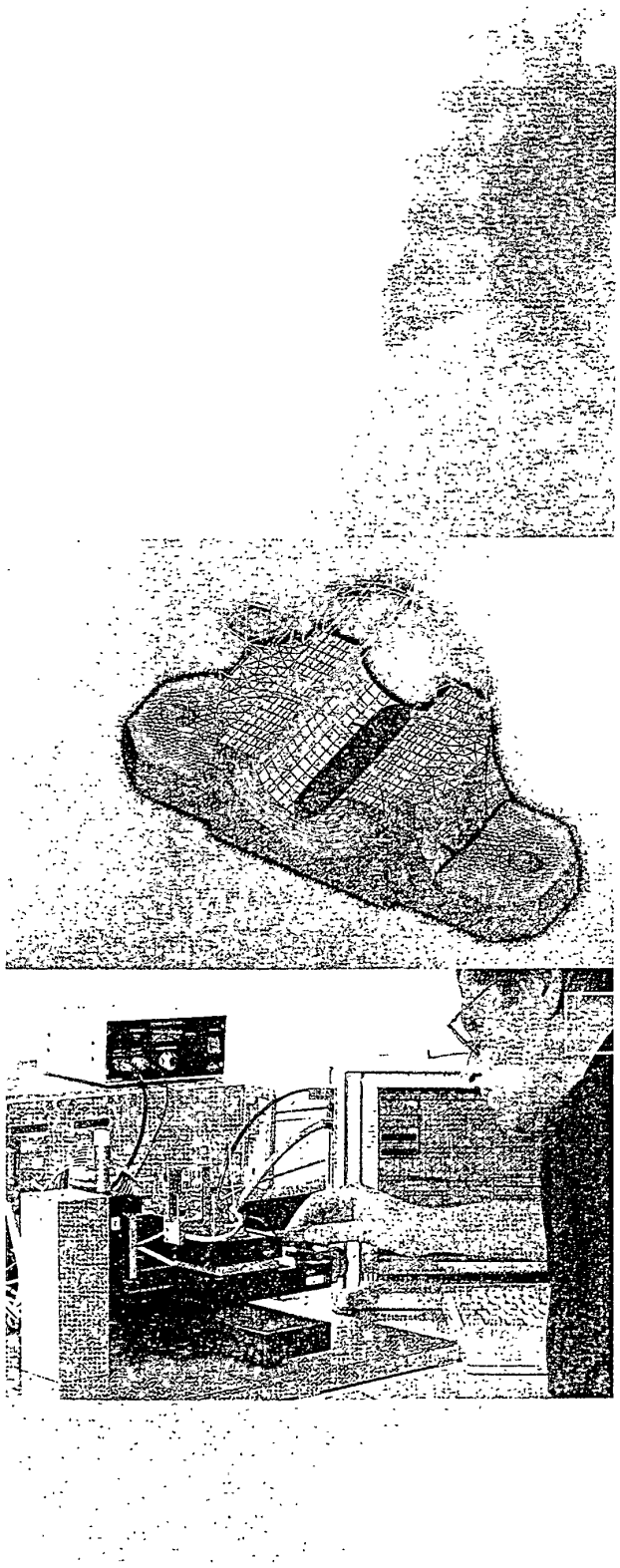
Aus Daten entstehen nützliche Informationen, wenn sie optimal in das Gesamtsystem integriert werden.

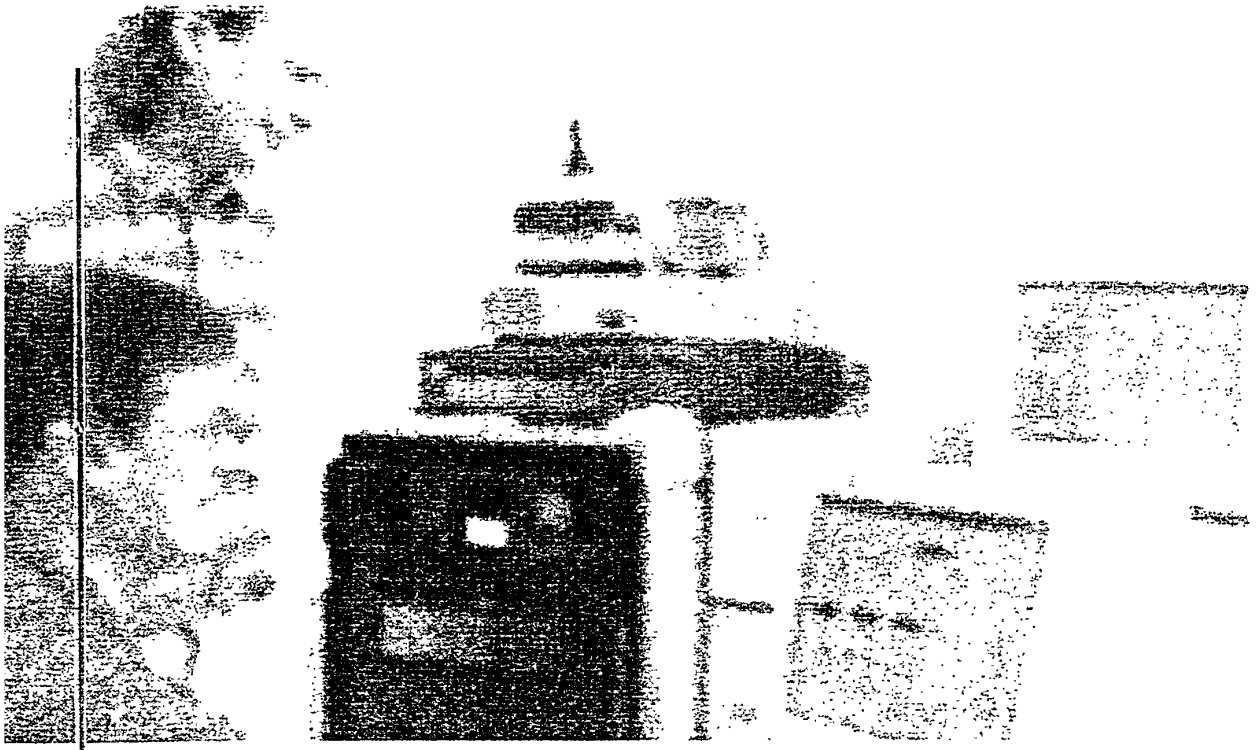
When data is optimally integrated in the entire system, useful information can be processed therefrom.

Computer Aided Engineering Services

Mit hochqualifizierten, computerbasierenden Dienstleistungen unterstützt das HSG-IMIT Industriebetriebe bei der effizienten und praktischen Lösung von Aufgaben in der Entwicklung, Konstruktion und Qualitätssicherung.
Das Team Modeling & Design bietet die Rechnersimulation beliebiger Objekte und ihres Verhaltens unter physikalischen Belastungen an. Die rationelle Qualitätssicherung ist das Ziel des TestPoint™-Services.
Beide Angebote basieren auf langer und praktischer Erfahrung und sind aus dem Bedarf des Instituts gewachsen.

With highly qualified, computer based services HSG-IMIT supports manufacturing facilities in the efficient and practical solutions of tasks in development, construction and quality assurance. The Modeling and Design team offers the computer simulation of chosen objects and their behavior under physical demands. Efficient quality assurance is the goal of the TestPoint™ service.
Both items are based on long, practical experience and have grown out of the institute's own needs.





Modeling & Design

www.hsg-imit.de

Simulation spart Entwicklungsaufwand.

Simulation reduces development time and costs.

Mit Hilfe der Finite Elemente Methode (FEM) unterstützt das Team Modeling & Design des HSG-IMIT Konstrukteure und Entwickler bei ihren vielfältigen Aufgaben. Jeder vorstellbare Körper kann im Rechner simuliert und auf die verschiedenen physikalischen Belastungen untersucht werden.
Der Service verkürzt Entwicklungszeiten, erklärt Funktionsmängel, spart Musterbauten und Material.

With the help of the Finite Element Method (FEM), the Modeling and Design team assists the HSG-IMIT constructors and developers in their many faceted work. Any imaginable physical substance can be simulated on the computer and its various physical characteristics tested. This service saves development time, explains functional deficiencies and saves on material and the time required for building prototypes.

Measurement Automation

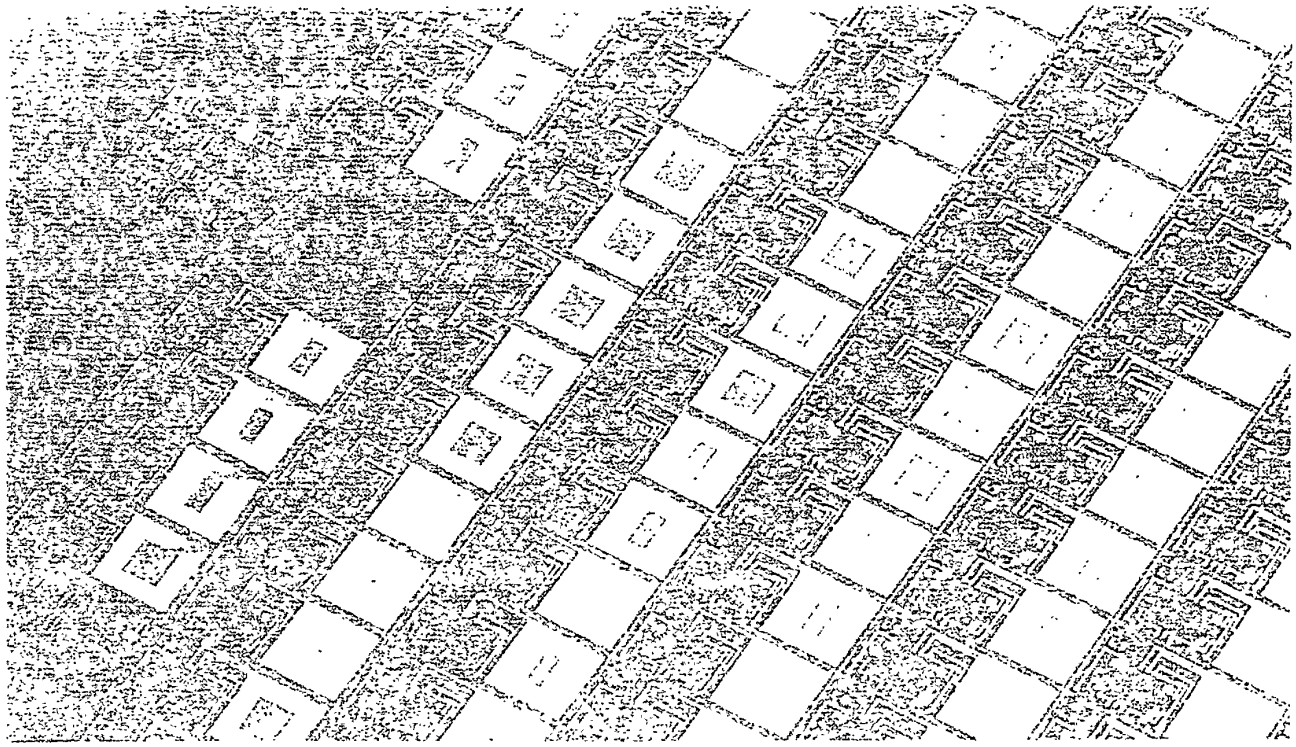
www.hsg-imit.de

Automatisierte Qualitätssicherung mit Hilfe des TestPoint™-Angebots.

Automated quality assurance assisted by TestPoint™.

Mit dem Angebot von TestPoint™-Service antwortet das HSG-IMIT auf die Herausforderungen der Qualitätssicherung. Das TestPoint™-Team plant, programmiert und betreut automatisierte Prüfstände für industrielle Partner.
Qualitätssicherung wird komfortabler, kompatibler zur Produktionsumgebung und über das Internet kontrollierbar.

HSG-IMIT's TestPoint™ service is their answer to the challenges of quality assurance. The TestPoint™ team plans and programs automated test benches and provides consultation for industrial partners. Quality assurance therefore, becomes more convenient and more compatible to the production environment and can be controlled over the internet.



Das HSG-IMIT produziert im eigenen Reinraumlabor mit der Bulk-Silizium-Mikromechanik. Dieses Verfahren verändert Siliziumwafer in ihrer Dicke und arbeitet die Bauteile eines geplanten Sensors oder Fluidikelements schichtweise aus der Oberfläche des Materials heraus. Erfahrung in der speziellen Prozesstechnik und der Präzisionsgrad dieses Verfahrens führen zu schnellen, zuverlässigen Ergebnissen bei der Entwicklung und Herstellung von Mikrosystemtechnik.

Using the bulk-silicon-micromechanics procedure HSG-IMIT manufactures in its own clean room labratory. Components such as sensors or fluidic elements are formed in layers out of the silicon wafer. Experience in this specialized process technology and the degree of precision in this procedure lead to fast reliable results in the development and production of microsystem technology.

Waferprocessing

www.hsg-imit.de

Einsatz modernster Hochtemperatur- und Vakuumverfahren.

Use of the latest hightemperature and vacuum processes.

Karten mit Transponderchip, die berührungslos mit Automaten, Kontroll- und Abrechnungsstellen kommunizieren, finden breite Anwendungsmöglichkeiten. Durch ein am HSG-IMIT entwickeltes Verfahren lassen sich die Chips direkt auf den Kunststoffkarten mit ihrer Antenne verlöten. Im 0,3-Sekundentakt erzeugen temperaturgeregelte Laserstrahlen stabile Mikrolötverbindungen. Das laserunterstützte Flip-Chip-Bonden ermöglicht Anwendern die kostengünstige Massenproduktion von Chipkarten, Smart Labels und Multifunktionskarten.

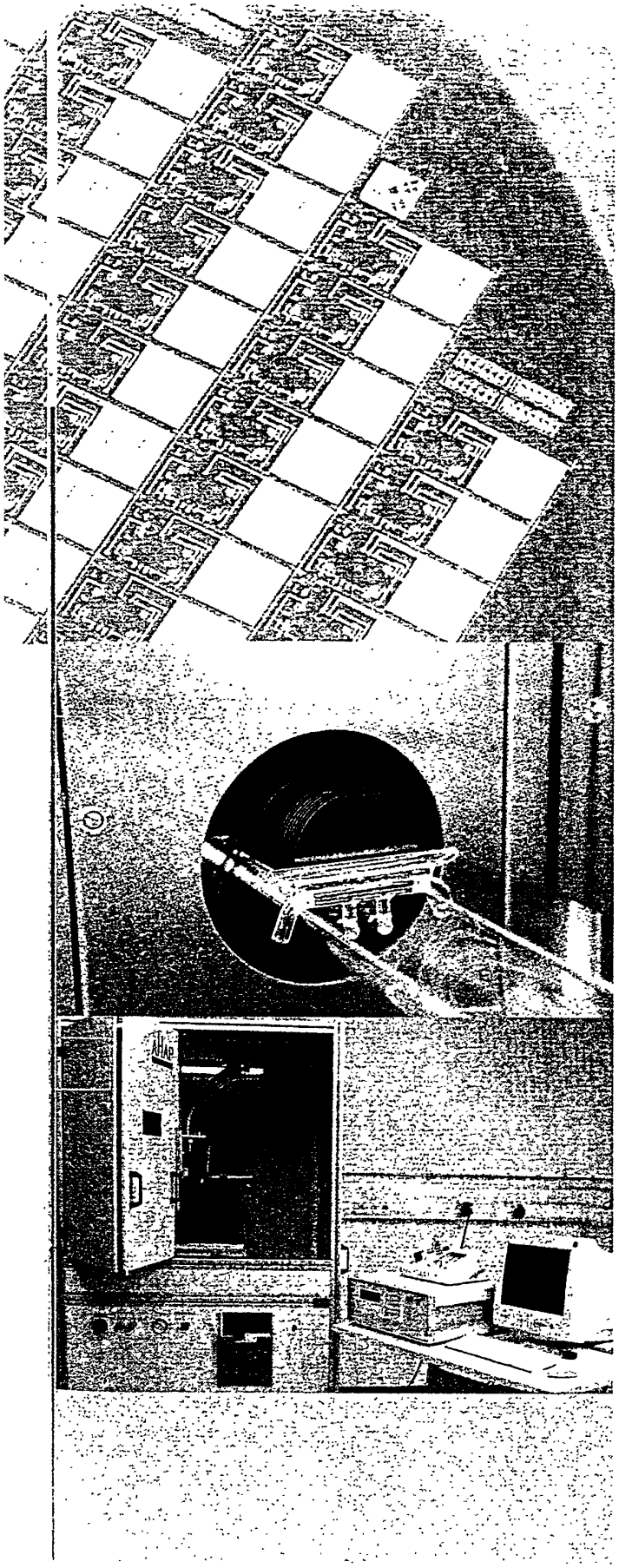
Cards with transponder chips which are capable of communicating, without physical contact, with automatons, control and calculation stations have a wide range of useful applications. Through a procedure developed by HSG-IMIT, chips can be directly soldered, with their antennas, to the plastic cards. In 0.3 second intervals temperature controlled laser beams produce stable micro-soldered bonds. The laser assisted Flip-Chip Bonding enables the cost-effective mass production of chipcards, smart labels and multifunction cards.

Chipcard Technology

www.hsg-imit.de

Neue Aufbau- und Verbindungstechnik für Chipkarten – Laser-Mikrolöten.

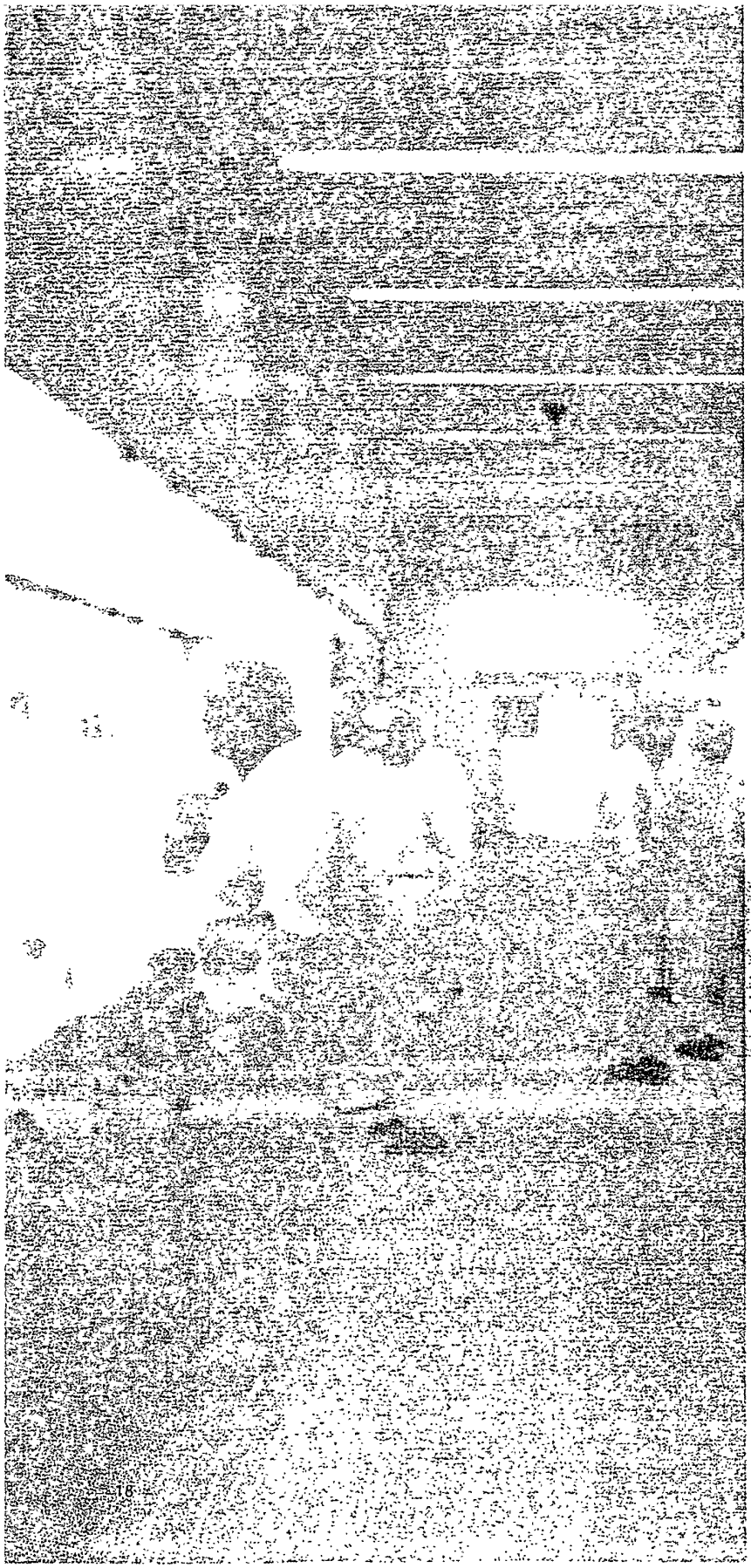
New assembly and bonding technique for chipcards – Laser micro-soldering.



Production & Prototyping

Bei jeder Innovation stellt sich die Frage nach der Serienproduktion. Beim HSG-IMIT steckt die Antwort bereits im Angebot. Als Dienstleister für die Industrie betrachten wir die gesamte Wertschöpfungskette von der Idee bis zur Produktion. Ausstattung, Kapazitäten und Kernkompetenzen des Instituts, seines Reinraumes und der nachgeschalteten Fertigungseinrichtungen sind darauf ausgerichtet, mikrotechnische Komponenten und Systeme in kleinen und mittelgroßen Serien herzustellen. Gemeinsam mit industriellen Partnern organisiert das HSG-IMIT die Massenfertigung und spezielle Lösungen in großen Produktionsstätten der Mikrosystemtechnik, den sogenannten Foundries.

Every innovation has the inherent question of how it can be realized for series production. At the HSG-IMIT the answer is already in the offer. Being a complete service provider for the industry we consider the entire value chain. That means from idea conception through to its implementation. Equipping, capacities and core competencies of the institute, its clean rooms and the connected production facilities are all designed for the small and medium sized mass production of micro technical components and systems. Working together with industrial partners, HSG-IMIT arranges the mass production and specialized solutions in large microsystem technology manufacturing facilities, so-called foundries.



Das 600 m² große Reinraumlabor dient dem HSG-IMIT als voll ausgestattete Entwicklungs- und Produktionsstätte. In sieben Reinraum-Abschnitten finden sämtliche Arbeitsschritte ihren Platz. Das Leistungsspektrum reicht von der Siliziumwafer-Bearbeitung über Musteraufbau und Messtechnik bis zur Qualitäts- und Funktionskontrolle. Das HSG-IMIT und seine Partner beherrschen darüber hinaus die Verarbeitung von Glas, Kunststoffen und speziellen Metallen. Fertigungseinrichtungen ermöglichen die Kleinserienproduktion im direkten Kundenauftrag sowie im Rahmen von Forschungs- und Entwicklungsprojekten.

The 600 sq. m. clean room laboratory serves the HSG-IMIT as fully equipped development and production facility. All of the various tasks take place in seven linked clean room segments. The range of tasks performed, begins with silicon wafer processing includes prototype construction and measurement technology and continues to quality and function control. In addition, HSG-IMIT and its partners have complete command of glass, plastic and special metal processing. Production facilities enable small lot production for direct customer contracts as well as in the framework of research and development projects.

Entwicklungs- und Produktionsstätte zugleich: das Reinraumlabor.

The clean room laboratory: both development and production facility.

Reinraumklasse 10 bis 100 unter
Laminar Flow
Servicebereich Klasse 10.000
250 m² Weissbereich
170.000 m³/h Luftumsatz, davon 30.000 m³ Frischluft
1 m³/h DI-Wasseraufbereitung
Verarbeitungskapazität: 10.000 Wafer/Jahr

Das Service- und Produktionsangebot im Reinraumlabor des HSG-IMIT umfasst im Bereich der Wafertechnologie:

Fotolithografie
- Vorder- zu Rückseiten-Justierung
- Standard-Auflösung 5 µm (möglich bis 2 µm)
- Positiv- und Negativ-Prozess

Chemical Vapor Deposition (CVD)
Abscheiden von dünnen Schichten aus der Dampfphase
- Poly-Silizium, auch in-situ dotiert
- Low Temperature Oxide (LTO)
- Siliziumnitrid
- Thermische Oxide, Dotierung

Physical Vapor Deposition (PVD)
- Aufdampfen
- Sputtern
  - Metalle
  - Dielektrika

Strukturierung
- nasschemisches Ätzen
  - isotrop
  - anisotrop (Silizium)
- trockenchemisches Ätzen (RIE, ASE™)

Messtechnik
- Charakterisierung von Schichten und Oberflächen
  - Ellipsometrie (Dicke, Brechzahl)
  - Weisslicht-Interferometrie
  - Rasterelektronenmikroskopie

Waferbonden für Mehrlagenaufbauten
- anodisches Bonden
- Silicon-on-Insulator-Bonden
- Silicon-direct-Bonden
- selektives Verbinden strukturierter Wafer

Sägen
- Single Wafer
- Si-Si-Pakete
- Si-Pyrex(Glas)-Si-Pakete

Clean room classification of 10 - 100 in
laminar flow
Service range class 10,000
250 m² white area
170.000 m³/h air exchange, therefrom 30,000 m³ fresh air
1 m³/h DI-water treatment
Processing capacity: 10,000 wafer/year

The range of services and the products manufactured in the clean room using wafer technology comprises:

Photolithography
- Front to back alignment
- Standard resolution 5 µm (possible up to 2 µm)
- Positive and negative process

Chemical Vapor Deposition (CVD)
Depositing of thin layers out of the vapor phase
- Poly-silicon, also in-situ doped
- Low Temperature Oxide (LTO)
- Silicon nitride
- Thermal oxide, doping

Physical Vapor Deposition (PVD)
- Vapor deposition
- Sputtering
  - Metals
  - Dielectrics

Structuring
- Wet chemical etching
  - Isotropic
  - Anisotropic (Silicon)
- Dry chemical etching (RIE, ASE™)

Measurement Technology
- Characterization of layers and surfaces
  - Ellipsometry (thickness, refractive index)
  - White light interferometry
  - Scanning electron microscopy

Waferbonding for multilayers
- Anionic bonding
- Silicon-on-Insulator bonding
- Silicon direct bonding
- Selective bonding of structured wafers

Sawing
- Single wafer
- Si-Si-sandwich
- Si-Pyrex(glass)-Si-sandwich

Marketing & Consulting Services

Von der Idee zur Produktion – so lautet das Handlungsmotto des HSG-IMIT für die Produktentwicklung in der Mikrosystem- und Informationstechnik. Sie als Kunde und Entwicklungspartner können jedoch schon bei der Ideenfindung auf uns zählen und erhalten auch nach der eigentlichen Projektlaufzeit weitere Unterstützung aus einer Hand.

Aus unserer Erfahrung im Bereich der Auftragsforschung wissen wir, dass Innovationen oft aus Synergien entstehen und kreative Teamarbeit nicht selten ungewöhnliche Lösungen bringt. Darum vermitteln wir Ihnen zum Beispiel gerne Verbundpartner – selbstverständlich unter Wahrung der Vertraulichkeit. In Workshops bieten wir Ihren Gedanken und Visionen ein Forum. Bei diesen Gelegenheiten und darüber hinaus als Mitglied der Hahn-Schickard-Gesellschaft treffen Sie Gleichgesinnte, die die Chancen neuer Technologien und neuer Märkte nutzen wollen.

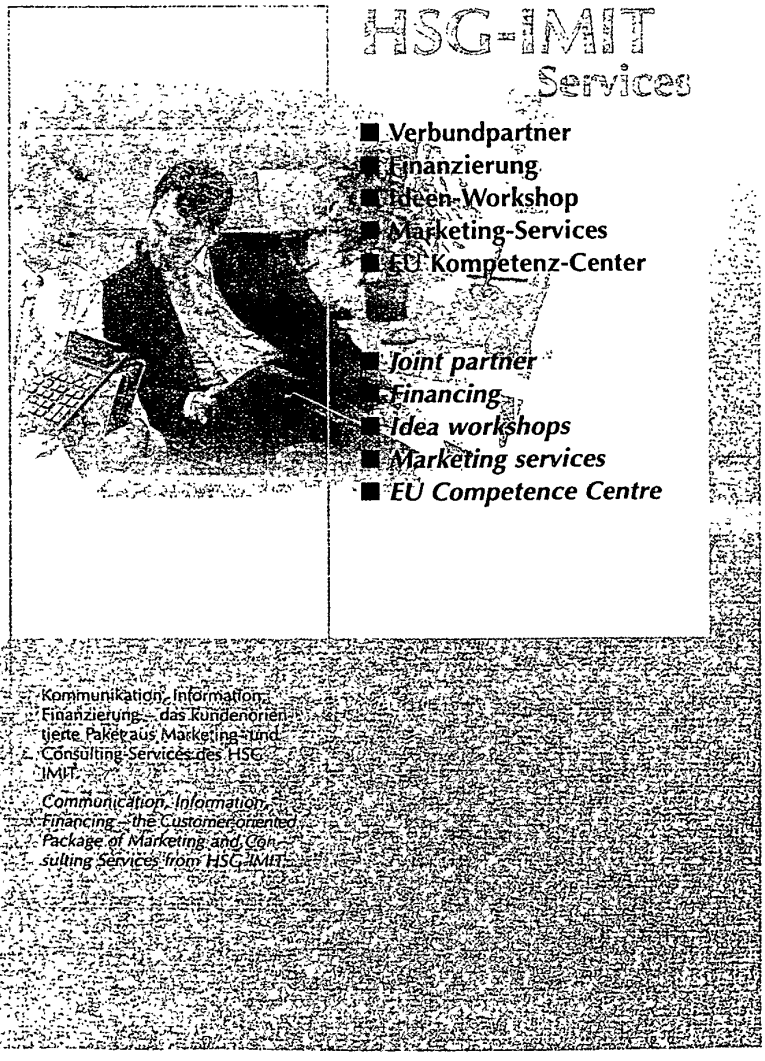
Als Liquid Handling Kompetenz-Center der Europäischen Kommission bieten wir Beratungstätigkeiten an. Wir können für Sie vielfältige Kontakte knüpfen und Fachinformationen beschaffen. Weitere Informationen zum Leistungsangebot entnehmen Sie bitte unserer Internet-Seite.

Das HSG-IMIT vermittelt im Rahmen der Projektberatung Verbundprojekte, die anteilig von öffentlichen Forschungsprogrammen mit getragen werden. Nutzen Sie unsere Erfahrungen in der Beantragung von Fördermitteln.

Den Bereich Finanzierung werden wir stärken und privatwirtschaftliche, intelligente Finanzierungsmethoden mit Hilfe renommierter Partner anbieten.

Suchen Sie Informationen über den Markt, auf dem Sie demnächst starten wollen? In dieser Phase steht Ihnen das HSG-IMIT mit seinen Partnern ebenfalls zur Verfügung. Gemeinsam mit Ihnen legen wir heute den Grundstein für Ihren künftigen Erfolg.

From the idea to production – that is HSG-IMIT's motto for product development in microsystem and information technologies. As client and development partner however you can count on us as early as during idea creation. Likewise, we offer our support after the duration of the project. One source for all of your needs.



Kommunikation, Information, Finanzierung – das kundenorientierte Paket aus Marketing- und Consulting-Services des HSG-IMIT.

Communication, Information, Financing – the Customer-oriented Package of Marketing and Consulting Services from HSG-IMIT.

Unser Markt weltweit
Our Market worldwide

From our experience in committed research we know that innovations often occur through collaboration and that unusual solutions are not seldom born of team work.
For this reason we gladly procure associates – of course with guaranteed confidentiality. We also offer your thoughts and visions a forum in our workshops. Through these opportunities as well as a membership in the Hahn-Schickard-Gesellschaft you can meet others who are like-minded and wanting to take advantage of the chances offered by the new technologies and markets. As Liquid Handling Competence Centre for the European Commission, we can offer you consulting services and provide you with various new contacts and specialist information. Further information concerning this offer is available in our internet site.
The HSG-IMIT mediates, within the framework of the project consulting, joint projects which are partly funded by public research programs. Take advantage of our experience in applying for subsidies. We will strengthen the financial side of the project with aid from the private sector, applying intelligent financing methods with the assistance of noted partners. Are you in need of information concerning your prospective market? In this phase as well, HSG-IMIT is ready with its partners to assist you. Together we will lay the corner stone today for your future success.

Über Grenzen hinauswachsen und dabei nicht den Ursprung aus den Augen verlieren – so sehen wir unsere Globalisierungsstrategie. So umfangreich dieser Anspruch ist, so unterschiedlich sind unsere Kunden. Hierzu gehören genauso Global Player wie die Siemens AG, bekannte Mittelständler wie Festo AG in Esslingen, Eppendorf AG in Hamburg, Hoerbiger Origa in Filderstadt und aus unserer Region: Marquardt, SCHMIDT Feintechnik oder Kundo Systemtechnik.
Ganz gleich, ob Sie sich dafür entschieden haben, den heimischen Markt zu beliefern oder weltweit aufzutreten, wir möchten Ihnen zeigen, wie konstruktiv, erfolgreich und marktorientiert eine Zusammenarbeit mit unserem Institut sein kann. Nehmen Sie direkt Kontakt auf!

Growing over our frontiers and, at the same time, not loosing sight of our origin – that is how we define our globalization strategy. An extensive strategy with a broad range of demands corresponding to our clientele: global players such as Siemens AG, well-known medium-sized companies like Festo AG in Esslingen, Eppendorf AG in Hamburg, Hoerbiger Origa in Filderstadt and from our region: Marquardt, SCHMIDT Feintechnik or Kundo Systemtechnik. Regardless if you have decided on a domestic market or the global market, we would like to show you how constructive, successful, and market oriented working together with our institute can be. Contact us today!

Direktkontakt
Contacts

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Das HSG-Institut für Feinwerk- und Zeitmesstechnik erreichen Sie in Stuttgart unter folgender Adresse:

The HSG-Institute for Precision Engineering in Stuttgart could be reached under the following address:

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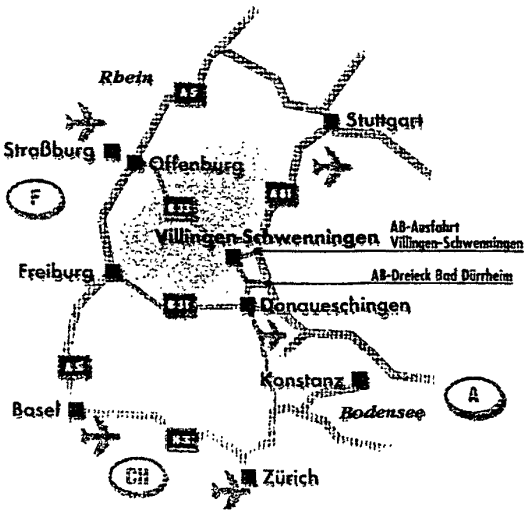
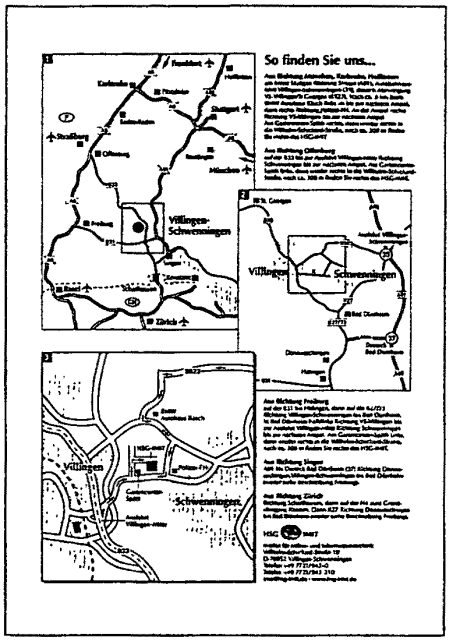
eMail hsg-ifz@izfm.uni-stuttgart.de
www.uni-stuttgart.de/hsi

Das HSG-IMIT liegt mitten in der südwestdeutschen Hightech-Landschaft und auf dem halben Weg zwischen Stuttgart und Zürich. Der Standort Villingen-Schwenningen ist über die Autobahn A 81 und die Bundesstraßen B 27 und B 33 erreichbar sowie über die Bahnlinien Offenburg- bzw. Konstanz-Villingen und Stuttgart- bzw. Zürich-Rottweil. Die nächstgelegenen Flugplätze sind in Schwenningen und in Donaueschingen. Von den Flughäfen Zürich und Stuttgart aus dauert die Autofahrt ca. 1,5 Stunden. Vor Ort finden Sie das Institut zwischen den beiden Stadtbezirken Villingen und Schwenningen.

The HSG-IMIT is located in the middle of the southwest German high tech scene, halfway between Stuttgart and Zurich in Villingen-Schwenningen. Easy to reach via the A 81 autobahn and the federal highways B 27 and B 33; or by rail, Offenburg-Constance to Villingen or the Stuttgart-Zurich to Rottweil line. The closest airports are in Schwenningen and Donaueschingen From either of the international airports of Stuttgart or Zurich, we can be reached by car in approximately 1.5 hours. We are located between the two municipalities of Villingen and Schwenningen.





Falls Sie uns besuchen möchten: Eine detaillierte Wegbeschreibung finden Sie im Internet (siehe unten) oder auf einem Infoblatt, das wir Ihnen gerne zufaxen.

If you would like to visit us we would gladly send you an easy to follow and detailed description of the directions per fax or you may obtain them from our internet site.

„HSG-IMIT Finder"

www.hsg-imit.de : 4600

Erläuterung der „Finder-Nr." siehe Seite 6.

For explanation of the „finder number" see page 6.