

(54) **FOCUSING OF MICROPARTICLES IN MICROFLUIDIC SYSTEMS**

(75) Inventors: **H. Garrett Wada**, Atherton, CA (US); **Anne R. Kopf-Sill**, Portola Valley, CA (US); **Marja Liisa Alajoki**, Palo Alto, CA (US); **J. Wallace Parce**, Palo Alto, CA (US); **Benjamin N. Wang**, Palo Alto, CA (US); **Andrea W. Chow**, Los Altos, CA (US); **Robert S. Dubrow**, San Carlos, CA (US)

5,593,838 A	1/1997	Zanzucchi et al.	
5,603,351 A	2/1997	Cherukuri et al.	
5,608,519 A	3/1997	Gourley et al.	
5,635,358 A	6/1997	Wilding et al.	
5,637,469 A	6/1997	Wilding et al.	
5,699,157 A	12/1997	Parce	
5,739,902 A *	4/1998	Gjelsnes et al.	356/73
5,750,015 A	5/1998	Soane et al.	
5,779,868 A	7/1998	Parce et al.	
5,800,690 A	9/1998	Chow et al.	
5,842,787 A	12/1998	Kopf-Sill et al.	

(List continued on next page.)

(73) Assignee: **Caliper Technologies Corp.**, Mountain View, CA (US)

FOREIGN PATENT DOCUMENTS

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

WO	WO 96/04547	2/1996
WO	WO 97/02357	1/1997
WO	WO 98/00231	1/1998
WO	WO 98/00705	1/1998

(List continued on next page.)

(21) Appl. No.: **09/569,747**

OTHER PUBLICATIONS

(22) Filed: **May 11, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/134,472, filed on May 17, 1999.

Cohen, C.B. et al., "A Microchip-Based Enzyme Assay for Protein Kinase A," *Anal. Chem.* (1999) 273:89-97.
Dasgupta, P.K., et al. "Electroosmosis: A Reliable Fluid Propulsion System for Flow Injection Analysis," *Anal. Chem.* (1994) 66:1792-1798.

(List continued on next page.)

(51) **Int. Cl.**⁷ **G01N 7/00**

(52) **U.S. Cl.** **436/148**; 436/34; 436/52; 436/180; 436/518; 422/50; 435/91.1

(58) **Field of Search** 436/148, 34, 52, 436/180, 518; 422/50; 204/452, 454, 600; 356/73; 435/7.1, 6, 287.3, 91.1; 210/634

Primary Examiner—Jill Warden
Assistant Examiner—Brian Sines
(74) *Attorney, Agent, or Firm*—Andrew L. Filler

(56) **References Cited**

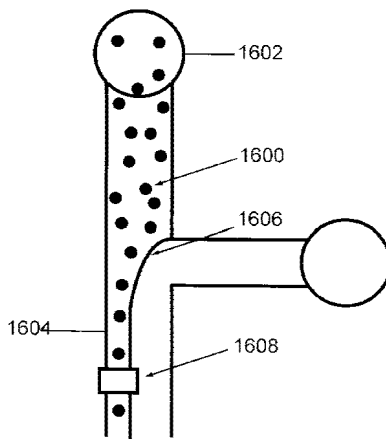
(57) **ABSTRACT**

U.S. PATENT DOCUMENTS

4,390,403 A	6/1983	Batchelder	
4,793,705 A	12/1988	Shera	
4,844,610 A *	7/1989	North, Jr.	356/73
4,908,112 A	3/1990	Pace	
5,126,022 A	6/1992	Soane et al.	
5,498,392 A	3/1996	Wilding et al.	
5,571,410 A	11/1996	Swedberg et al.	
5,585,069 A	12/1996	Zanzucchi et al.	
5,587,128 A	12/1996	Wilding et al.	

Methods and systems for particle focusing to increase assay throughput in microscale systems are provided. The invention includes methods for providing substantially uniform flow velocity to flowing particles in microfluidic devices. Methods of sorting members of particle populations, such as cells and various subcellular components are also provided. Integrated systems in which particles are focused and/or sorted are additionally included.

35 Claims, 22 Drawing Sheets



U.S. PATENT DOCUMENTS

5,852,495	A	12/1998	Parce	
5,858,187	A *	1/1999	Ramsey et al.	204/452
5,869,004	A	2/1999	Parce et al.	
5,876,675	A	3/1999	Kennedy	
5,879,625	A *	3/1999	Roslaniec et al.	422/50
5,880,071	A	3/1999	Parce et al.	
5,882,465	A	3/1999	McReynolds	
5,885,470	A	3/1999	Parce et al.	
5,942,443	A	8/1999	Parce et al.	
5,948,227	A	9/1999	Dubrow	
5,955,028	A	9/1999	Chow	
5,957,579	A	9/1999	Kopf-Sill et al.	
5,958,203	A	9/1999	Parce et al.	
5,958,694	A	9/1999	Nikiforov	
5,959,291	A	9/1999	Jensen	
5,964,995	A	10/1999	Nikiforov et al.	
5,965,001	A	10/1999	Chow et al.	
5,965,410	A	10/1999	Chow et al.	
5,972,187	A	10/1999	Parce et al.	
5,972,622	A *	10/1999	Desjardins	435/7.1
5,972,710	A	10/1999	Weigl et al.	
5,976,336	A	11/1999	Dubrow et al.	
5,989,402	A	11/1999	Chow et al.	
6,001,231	A *	12/1999	Kopf-Sill	204/454
6,004,515	A	12/1999	Parce et al.	
6,011,252	A	1/2000	Jensen	
6,012,902	A	1/2000	Parce	
6,042,710	A	3/2000	Dubrow	
6,046,056	A	4/2000	Parce et al.	
6,049,380	A	4/2000	Goodwin et al.	
6,068,752	A	5/2000	Dubrow et al.	
6,607,157		5/2000	Altendorf	
6,071,478	A	6/2000	Chow	
6,074,725	A	6/2000	Kennedy	
6,080,295	A	6/2000	Parce et al.	
6,120,666	A *	9/2000	Jacobson et al.	204/452
6,150,119	A *	11/2000	Kopf-Sill et al.	435/7.1
6,267,858	B1 *	7/2001	Parce et al.	204/600

FOREIGN PATENT DOCUMENTS

WO	WO 98/00707	1/1998
WO	WO 98/02728	1/1998
WO	WO 98/05424	2/1998
WO	WO 98/22811	5/1998
WO	WO 98/45481	10/1998
WO	WO 98/45929	10/1998

WO	WO 98/46438	10/1998
WO	WO 98/49548	11/1998
WO	WO 98/55852	12/1998
WO	WO 98/56956	12/1998
WO	WO 99/00649	1/1999
WO	WO 99/10735	3/1999
WO	WO 99/12016	3/1999
WO	WO 99/16162	4/1999
WO	WO 99/19056	4/1999
WO	WO 99/19516	4/1999
WO	WO 99/29497	6/1999
WO	WO 99/56954	11/1999
WO	WO 00/09753	2/2000

OTHER PUBLICATIONS

- Jacobson, S.C. et al., "Fused Quartz Substrates for Microchip Electrophoresis," *Anal. Chem.* (1995) 67:2059-2063.
- Kessler J., "Hydrodynamic focusing of motile algal cells" *Nature* vol. 313 pp. 218-220.
- Knight J., et al., "Hydrodynamic Focusing on a Silicon Chip: Mixing Nanoliters in Microseconds" *Physical Review Letters* (1998) vol. 80, No. 17 pp. 3863-3866.
- Kononenko and Shimkus "Non-equilibrium integral Doppler anemometric analysis of particel mixtures in a channel flow . . ." *J. of Chromatography* (1991) vol. 553 pp. 517-530.
- Manz, A. et al., "Electroosmotic pumping and electrophoretic separations for miniaturized chemical analysis systems," *J. Micromech. Microeng.* (1994) 4:257-265.
- Ramsey, J.M. et al., "Microfabricated chemical measurement systems," *Nature Med.* (1995) 1:1093-1096.
- Seiler, K. et al., "Planar Glass Chips for Capillary Electrophoresis: Repetitive Sample Injection, Quantitation, and Separation Efficiency," *Anal. Chem.* (1993) 65:1481-1488.
- Seiler, K. et al., "Electroosmotic Pumping and Valveless Control of Fluid Flow Within a Manifold of Capillaries on a Glass Chip," *Anal. Chem.* (1994) 66:3485-3491.
- Sundberg, S. A., "High-throughput and ultra-high-throughput screening: solution—and cell-based approaches," *Current Opinions in Biotechnology* 2000, 11:47-53.
- Watson, J. "The Early Fluidic and Optical Physics of Cytometry" *Cytometry* (1999) vol. 38 pp. 2-14.

* cited by examiner

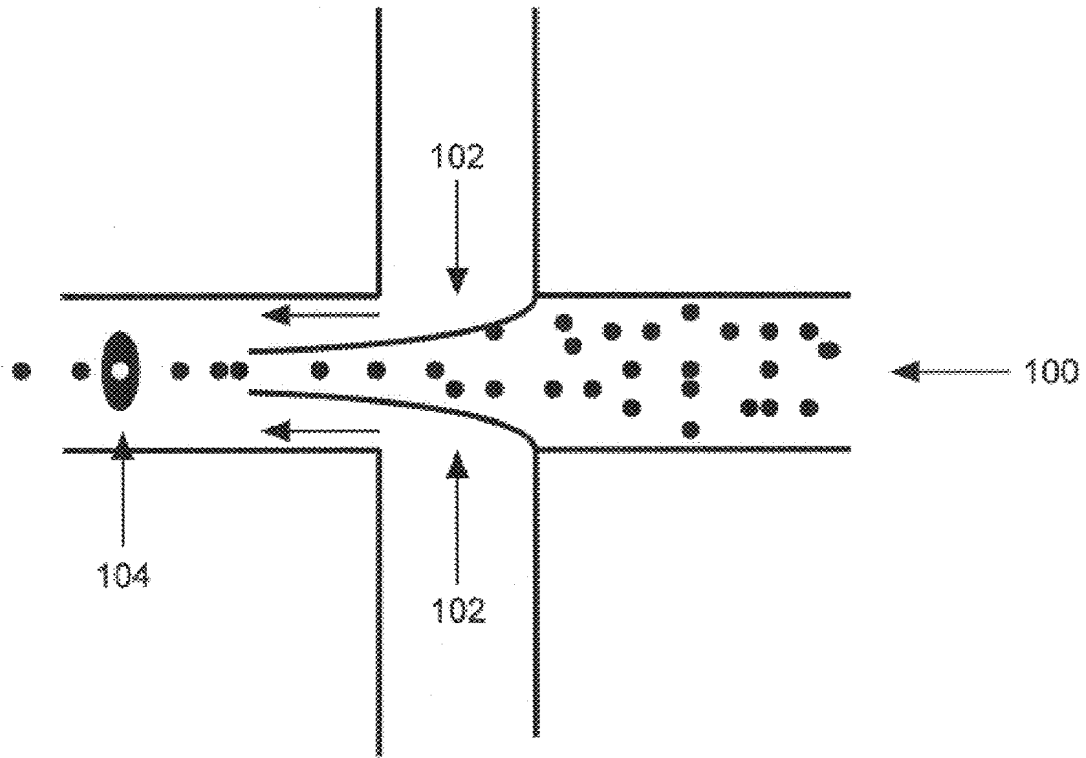


Fig. 1A

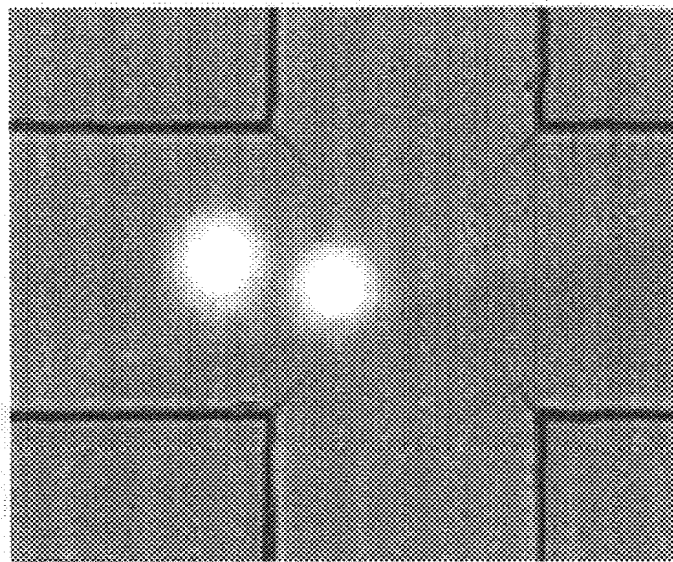


Fig. 1B

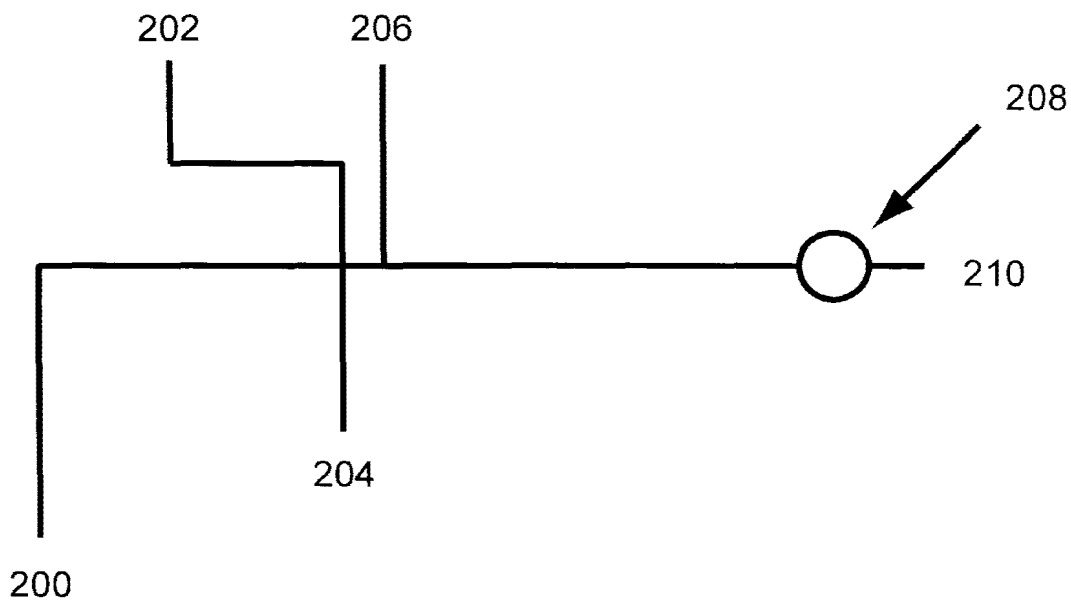


Fig. 2A

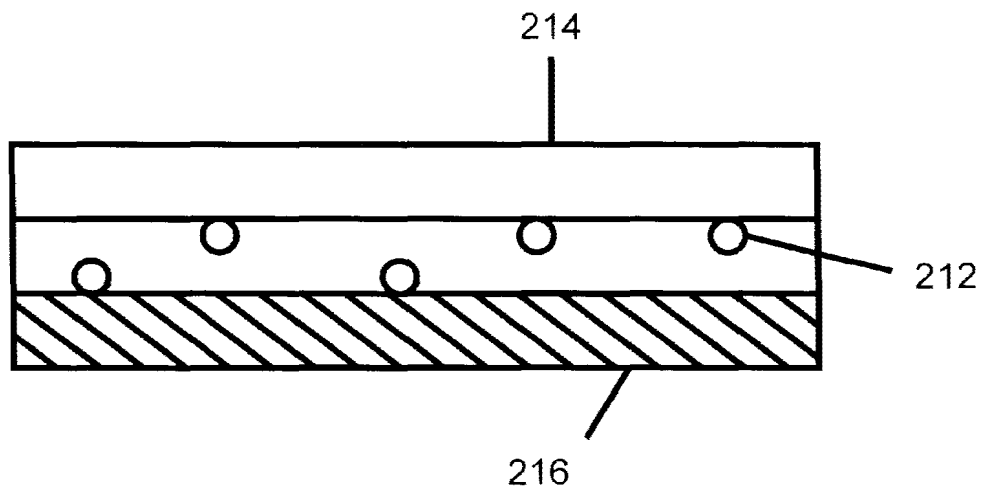


Fig. 2B

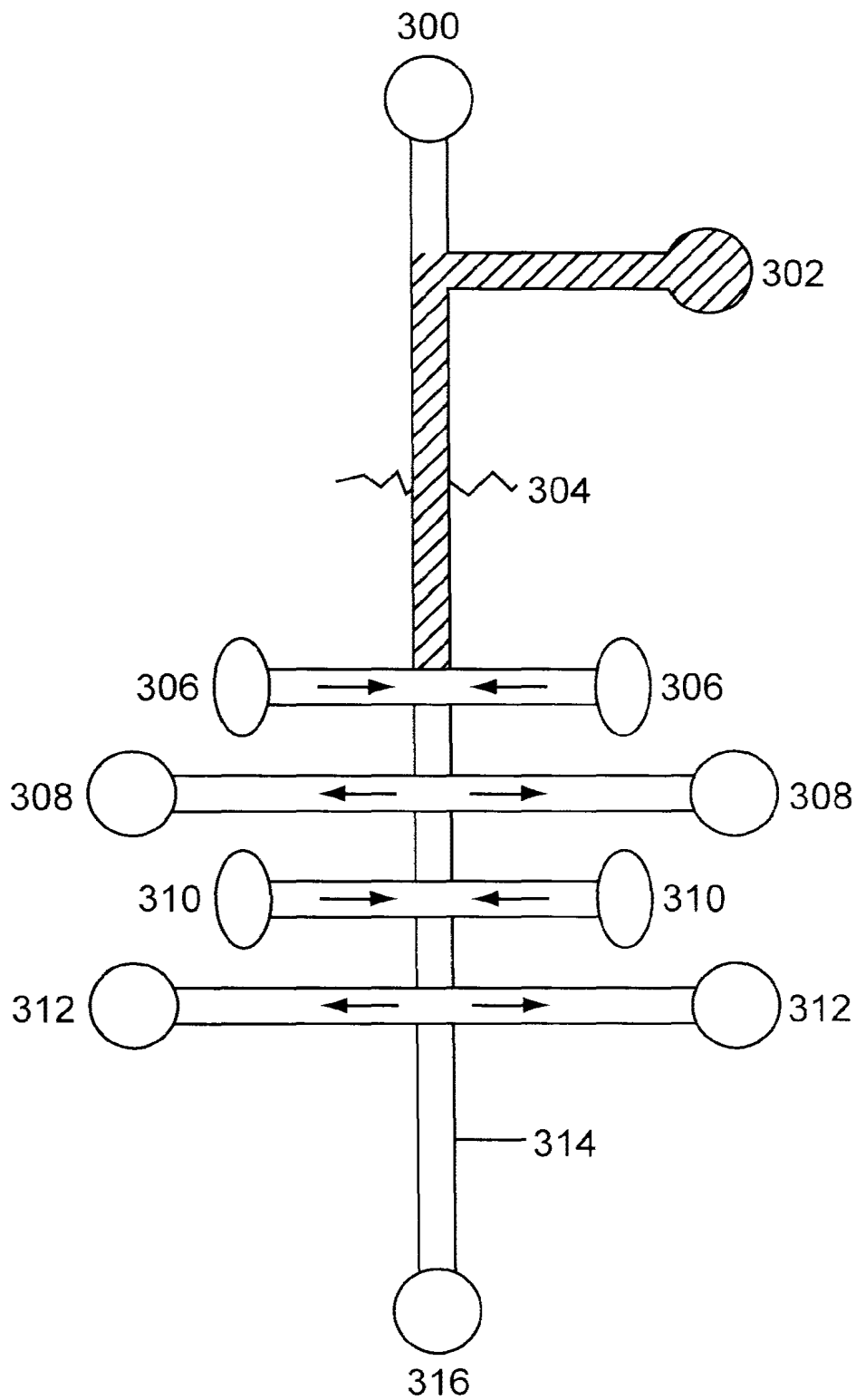


Fig. 3

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.