A Review of Single-Cell Manipulation Techniques for Microfluidic Lab-on-a-Chip Systems

Sean F. Romanuik and Bonnie L. Gray
School of Engineering Science, Simon Fraser University
8888 University Drive, Burnaby, BC, Canada V5A 1S6

Cell behavior is traditionally inferred from in vitro bulk measurements of large heterogeneous populations, yielding ensemble averages that obfuscate probes of discrete and intrinsic cellular properties[1-4]. Conversely, single-cell diagnostic methods directly probe each cell as an individual unto itself[1-2,4], facilitating finer studies of viability[5-6], pathogenesis[7-8], cell mechanics[9-11], links between biochemistry and cellular behavior[12-14], surface redox activity[15], cellular hydrodynamics[16], etc. Single-cell diagnostics also afford the quantification of population heterogeneity and facilitate the identification, characterization, and separation of subpopulations[17-18]. The most ubiquitous single-cell analysis method is flow cytometry (FC), which yields high-throughput, multiparameter analyses of individually probed cells[19-20]- facilitating identification of homogeneous subpopulations and studies of links between single- and multi-cell behaviour[4,21-22]. However, FC does not afford the tracking, manipulation, dynamic analysis, and subsequent retrieval of specific individual cells[23]. The other conventional single-cell diagnostic techniques (automated microscopy[24], laser scanning cytometry[25], capillary electrophoresis[26], and laser capture microdissection[27]) are low-throughput methods ill-suited to single-cell assays[23].

Advances in polymeric micro- and nano-fabrication afford increasingly sophisticated single-cell diagnostic tools[3,28-30]. In particular, microfluidic (MF) technologies offer several advantages over traditional tools, including: reduced material and power consumption; faster processing; portability; greater potential parallelization and integration; and lower fabrication costs[19,30]. Such MF technologies feature prominently in integrated lab-on-a-chip (LoC) and micro-total analysis system (μTAS) platforms[19,30]. Advances in LoC/μTAS technology promise high-throughput chips capable of tracking, manipulating, analyzing, and retrieving specific individual cells-satisfying applications beyond the capabilities of traditional techniques. As an example: our lab has been working towards an integrated LoC/μTAS device intended to trap cells in an array of physical single-cell traps, perform an immunobioassay identifying the cells secreting the antibodies of interest, and selectively retrieve those cells to create monoclonal cell lines producing said antibodies in large quantities[31-32].

The first step in developing such a LoC/μTAS device is to design a subsystem to manipulate individual cells, preferably to guide and hold them in arrays of reversible single-cell traps. This paper is primarily a critical review of advances in single-cell manipulation, relevant to such a LoC/μTAS platform. A wide variety of techniques will be examined, including: the magnetic trapping of labelled cells[33-37]; the manipulation of cells using optical tweezers[38-42]; the polarization and attraction/repulsion of cells via dielectrophoresis[43-46]; the manipulation of cells using the electromagnetic fields of surface plasmons[47-48]; and the trapping of cells in arrays of micro-scale wells[23,31-32,49-50], perfusive hydrodynamic traps[30,51-53], and microvortexes[54-55]. The potential for various single-cell analyses and the subsequent retrieval of cells afforded by each method shall be addressed.

References

[1]B.F. Brehm-Stecher et al., Microbiol. and Mol. Biol. Rev., **68**:538-559, 2004
[2]M.A. Witek et al., BioMEMS, 391-441, Eds. W. Wang and S.A. Soper, CRC, 2007
[3]C.E. Sims et al., Lab Chip, **7**:423-440, 2007
[4]H.M Shapiro, J. Microbiol. Methods, **42**:3-16, 2000
[5]M.R. Barer et al., Adv. Microb. Physiol., **41**:93-137,1999
[6]D. Rockabrand et al., Appl. Environ. Microbiol., **65**:4181-4188, 1999
[7]S.C. Kuo et al., Nature, **407**:1026-1029, 2000
[8]A. Strauβ et al., J. Bacteriol., **183**:3761-3769, 2001
[9]A.E. Smith et al., Proc. Natl. Acad. Sci. U.S.A., **97**:9871-9874, 2000
[10]X. Yao et al., Colloids Surf. Ser. B, **23**:213-230, 2002
[11]K.A. Schmitz et al., Biophys. J., **79**:468-478, 2000
[12]P. Cluzel et al., Science, **287**:1652-1655, 2000
[13]K.A. Kellerman et al., Dev. Biol., **208**:416-429, 1999
[14]R. Losick et al., J. Bacteriol., **181**:4143-4145, 1999
[15]C. Cai et al., Anal. Chem., **74**:114-119, 2002
[16]J.D. Pasteris et al., Chem. Geol., **180**:3-18, 2001
[17]T. Katsuragi et al., J. Biosci. Bioeng., **89**:217-222, 2000
[18]H. Stender et al., J. Microbiol. Methods, **48**:1-17, 2002
[19]C. Yi et al., Anal. Chim. Acta, **560**:1-23, 2006
[20]C. Yu et al., BioMEMS, 237-262, Eds. W. Wang and S.A. Soper, CRC, 2007
[21]F. Joux et al., Microbes Infect., **2**:1523-1535, 2000
[22]D.A. Veal et al.,J. Immunol. Methods,**243**:191-210,2000
[23]S. Lindström et al., Biochim. Biophys. Acta., **1810**:308-316, 2011
[24]M. Oheim, Br. J. Pharmacol., **152**:1-4, 2007
[25]M.M. Harnett, Nat. Rev. Immunol., **7**:897–904, 2007
[26]I.G. Arcibal et al.,Anal. Bioanal. Chem.,**387**:51-57,2007
[27]J. Kehr, Curr. Opin. Plant Biol., **6**:617-621, 2003
[28]G.M. Whitesides et al., Annu. Rev. Biomed. Eng., **3**:335-373, 2001
[29]H. Andersson et al., Curr. Opin. Biotechnol., **15**:44-49, 2004
[30]P.C.H. Li, Microfluidic Lab-on-a-Chip for Chemical and Biological Analysis and Discovery, CRC, 2006
[31]S.F. Romanuik et al., J.Med.Biol.Eng., **31**:121-127,2011
[32]S.F. Romanuik et al., IEEE Sensors J., **11**:2732-2739, 2011
[33]H. Lee et al., Appl. Phys. Lett., **85**:1063-1065, 2004
[34]V.I. Furdui et al., Lab Chip, **4**:614-618, 2004
[35]P. Grodzinski et al., Biomed. Microdev., **5**:303-310,2003
[36]D.W. Inglis et al., Appl. Phys. Lett., **85**:5093-5095, 2004
[37]K.H. Han et al., J. Appl. Phys., **96**:5797-5802, 2004
[38]S. Umehara et al., Biochem. Biophys. Res. Commun., **305**:534-240, 2003
[39]J. Enger et al., Lab Chip, **4**:196-200, 2004
[40]A.L.Birkbeck et al.,Biomed. Microdevices,**5**:47-54,2003
[41]P.Y. Chiou et al., Nature, **436**:370-372, 2005
[42]M.P. MacDonald et al., Nature,**426**:421-425,2003
[43]M. Durr et al., Electrophoresis, **24**:722-731, 2003
[44]Y. Huang et al., Anal. Chem., **74**:3362-3371, 2002
[45]J. Voldman et al., Anal. Chem., **74**:3984-3990, 2002
[46]F. Arai et al., Electrophoresis, **22**:283-288, 2001
[47]L. Huang et al., Optics Express, **17**:6018-6024, 2009
[48]D. Sinton et al., Microfluid. Nanofluid., **4**:107-116, 2008
[49]M. Charnley et al.,Integr. Biol. (Camb.),**1**:625-634,2009
[50]A.O. Ogunniyi et al., Nature Protocols, **4**:767-782, 2009
[51]D. Di Carlo et al., Lab Chip, **6**:1445-1449, 2006
[52]M.-C. Kim et al., J. App. Phys., **103**:044701, 2008
[53]S. Faley et al., Lab Chip, **8**:1700-1712, 2008
[54]D.T. Chiu, Anal. Bioanal. Chem., **387**:17-20, 2006
[55]C.M. Lin et al., Anal. Chem., **80**:8937-8945, 2008