Chapter 1
Microfluidics and Lab-on-a-Chip Devices: History and Challenges

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Abstract The rapid advances in microfabrication and nanofabrication in combination with the synthesis and discovery of new materials have propelled the drive to develop new technological devices such as smartphones, personal and tablet computers. These devices have changed the way humankind interacts and communicates and this change occurred very quickly due in part to decreased production and commercialization costs. As a result, not only nations with powerful economies but also emerging economies and poor countries can get access to these technologies and experience new ways to interact and instantly communicate what is happening around us. Following the advances of all these communication devices as well as those in microfabrication and nanofabrication and the emergence of new materials, technologies such as lab-on-a-chip (LOC) and micro total analysis systems (microTAS) were also boosted, albeit at a slower pace. LOC and microTAS applications have principally been utilized in the biomedical, food and environmental fields. But lately they have also found their place in the synthesis of new chemical compounds and the fabrication of nanostructures. It has become obvious that the LOC and microTAS technologies need to join forces with those behind the new communication devices which provide sources of power, detection and data transmission complementing the features that lab-on-a-chip and microTAS platforms can offer. An increasing number of microfluidic-based devices, developed both in small start-ups and large pharmaceutical and biomedical companies, is being released and entering the market. This chapter offers an overview of the first events in the history of LOC and microTAS devices, the biggest achievements and the challenges that still need to be overcome in order to accelerate the use of this technology.

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1.1 History

The origin of microfluidics devices fabricated using the technology of micromechanics is usually associated with the late 1960s and the works on gas chromatography at Stanford University and the ink jet printer nozzles developed at IBM. But hundreds of years earlier, researchers were already curious about the information they could extract from body fluids and were trying to understand the behavior of liquids confined in small diameters. Hippocrates (400 BC), Galen (200 AD), and Theophilus (700 AD) among others were interested in analyzing urine samples as a means of interpreting the functions of the human body (Gazzaniga 1999; Kouba et al. 2007; Wallis 2000). They performed these analyses bedside and tried to match the color and appearance of urine with symptoms, mainly fever and psychiatric disturbances. They did not have the possibility to use microfluidic chips; instead, they investigated the urine samples in examination flasks known as "matulas" verifying the color and appearance of the sample (Wittern-Sterzel 2000). They even tried to standardize this analysis method by drawing diagrams and pictures of "matulas" of colored urine to be used as a diagnostic tool (Kouba et al. 2007).

Hundreds of years later, James Jurin, a British physician and natural philosopher (1684–1749), Jean Léonard Marie Poiseuille, a French physicist and physiologist, and Gotthilf Heinrich Ludwing Hagen (1791–1884), a German physicist and hydraulic engineer, worked on describing the behavior of fluids that were confined in glass containers of small diameters. They published their studies on capillarity, in the case of Jurin, and formulated the famous Hagen–Poiseuille equation that describes the pressure drop in a fluid flowing through a cylindrical pipe establishing the basis of the theory explaining the behavior of fluids at reduced scales.

Today, thanks to the advances in microfabrication and nanofabrication and the synthesis of new materials, researchers can confine fluids into microchannels or nanochannels instead of "matulas" and have theoretical tools and simulation software that help them predict and understand the behavior of fluids contained in microfluidic devices. Currently, not only body fluids but also cells, tissues and even a whole organ can be investigated inside microfluidic chips.

As mentioned above, thanks to the new fabrication methods and available tools, the end of the 1960s saw the development of a first prototype of a quadrupole GC/MS by Finnigan Instrument Corporation who delivered it to Stanford and Purdue University. This first instrument cost 100,000 USD and it was controlled by a minicomputer (Brock 2011). A couple of years later, following the idea of William Thomson (later knows as Lord Kelvin), who in 1867 patented the use of electrostatic forces to control the release of ink drops onto paper, in 1951, Siemens produced the first continuous inkjet printer used in medical strip chart recorders. Then, in 1976, researchers at IBM produced the first commercially available continuous forms of laser printers (Bassous et al. 1977).

In 1993, Andreas Manz published a fundamental article describing the fabrication of a miniaturized capillary electrophoresis-based chemical analysis system on a chip (Harrison et al. 1993). In this work, a microchip of 1 cm by 2 cm was micromachined in glass and electroosmotic pumping was employed to drive the fluid flow and perform electrophoretic separation on-chip.

Just 1 year after the publication of Manz's work, the first International Conference on Micro-Total Analysis Systems took place in Enschede, The Netherlands, and has since then strengthened its position as the premier forum for reporting the latest research results in microfluidics, Lab-on-a-Chip, microfabrication, nanotechnology, integration and detection technologies for life science and chemistry (www.cbmsociety.org).

In 1998, Professor George Whitesides, one of the leaders and more active members of the microfluidics and Lab-on-a-Chip community, published an article on the rapid prototyping of microfluidic systems in polydimethylsiloxane (PDMS). This publication described the design and fabrication of microfluidic chips in a transparent elastomeric material in less than a day using a photolithography technique. It had a large impact on the microfluidics community and pushed the field forward providing researchers with an easy and fast fabrication method that has been widely used in various studies (Duffy et al. 1998; Xia and Whitesides 1998).

Two years later, the group of Dr. Richard D. Fair at Duke University (USA), published an article on the rapid actuation of discrete liquid droplets accomplished by direct electrical control of the surface tension (Pollack et al. 2000). This is one of the first publications describing a liquid handling technology known as digital microfluidics. This handling technique allows a controlled manipulation of picoliter- to microliter-sized droplets independently addressed on an open array of electrodes. This new method had a huge impact on chemical and enzymatic reactions, DNA-based applications, immunoassays, clinical diagnostics, cell-based applications, and proteomics due to its flexible device geometry, simple instrumentation, and easy integration with other technologies (Choi et al. 2012).

Seven years later, a new fabrication method was published by Prof. Whiteside's group describing the use of paper as a new, portable, low-cost alternative for the development of bioassay microfluidic devices (Martinez et al. 2007). By patterning paper, Whitesides and coworkers created well-defined millimeter-sized channels and hydrophilic and hydrophobic zones enabling the transport of fluid to desired locations without the need for pumps due to the capillarity effect. This new fabrication method offered a cheap alternative for the development of biosensing platforms at a very low cost that could be applied in countries with limited resources (Yetisen et al. 2013). More details regarding the use of paper-based microfluidic devices can be found in Chap. 7.

A couple of years ago, a technology called 3D imprinting, developed in the early 1980s at Ultra Violet Products in California by Charles Hull, probed the possibility of fabricating miniaturized fluidic reactors for the chemical syntheses of secondary amines, gold nanoparticles, and large polyoxometalate clusters (Kitson et al. 2012). One of the more attractive features of this new technology is the possibility to fabricate devices with three-dimensional features in a quite simple way which is expected to help the manufacture of large-scale integrated multilayer devices and their standardization between laboratories. This could possibly start the third decade of microfluidic revolution (Gross et al. 2014; Lee 2013).

A clear example of the impact of the 3D imprinting technology can already be found in studies involving cells and organs-on-chips (Kim et al. 2008; Tasoglu et al. 2013; Young 2013). By using 3D printing, microfluidic environments mimicking the in vivo situation can be fabricated providing a “closer to reality” environment that is being used in pharmaceutical labs to evaluate new drug candidates. Recently, the idea of building a body-on-chip device has been presented (Moraes et al. 2013; van der Meer and van den Berg 2012). The idea involved connecting compartmentalized environments in which different cells are cultured to mimic multiple organs that will be interconnected or isolated depending of the application in order to recreate a human body. This will have a big impact on the biomedical field, offering researchers a new test tool where new medicines and treatments can be tested.

As will be shown throughout this book, microfluidics and lab-on-a-chip devices offer a long list of attractive advantages for research in numerous fields requiring a low consumption of sample and reagents, portability, low-energy consumption, rapid response and multiplexing analysis, etc. However, challenges regarding its application at a large scale, the possibility of work with bigger volumes, the fabrication of low-cost and user-friendly devices and its integration with other analytical techniques are issues that need to be solved in order to accelerate the irruption of these technologies in our daily lives in a manner similar to that of smartphones and personal computers. In fact, there are many recent reports of LOC devices integrated in smartphones. The idea is to connect the microfluidic devices with the smartphone and take advantage of the features available in the latter, i.e., the power source, data transmission, and optical detection system (Mark et al. 2012; Yetisen et al. 2014).

As will be seen in the chapters ahead, several strategies to overcome these challenges are being successfully implemented and resulting in the commercialization and fabrication of new microfluidic, lab-on-a chip and microTAS devices (Araci and Brisk 2014; Chin et al. 2012) as presented in Table 1.1.

Researchers that are interested in learning, discussing, and sharing experiences regarding the use of microfluidics have multiple options for this through journals, conferences, blogs, and forums focusing on microfluidics, some of which are presented in Tables 1.2 and 1.3. These alternatives offer a great environment to exchange ideas, tips, and experiences and hopefully create a community for starting new collaborations between scientists from different backgrounds (chemistry, physics, biology, material science). Such collaborations are one of the reasons that microfluidics has been able to expand its impact and should definitively increase this impact on our lives.

Table 1.1 Companies working on the design, fabrication and/or application of microfluidic, lab-on-a-chip and μTAS devices

Company	Product	Description	Link
abbott	i-STAT portable handheld	Detection of cardiac markers, blood gases, electrolytes, lactate, and clotting time. Wireless data transmission, requires 2–3 drops of blood to perform a test	http://www.abbottpointofcare.com/Products-and-Services/iSTAT-Handheld.aspx
Advanced Liquid Logic	LSD-100	Bioassay automation platform capable of simultaneously performing 4 enzymatic activity assays on 40 dried blood spot, use a digital microfluidic cartridge	http://www.liquid-logic.com/lsd-100
Agilent Technologies	2100 Bioanalyzer	Provides sizing, quantitation, and quality control of DNA, RNA, proteins, and cells on a single platform. Requires 1–4 mL	http://www.genomics.agilent.com/en/Bioanalyzer-System/2100-Bioanalyzer-Instruments/?cid=AG-PT-106&tabId=AG-PR-1001
Alere	Afinion™ test	Microfluidic cartridge for measurement of glycated hemoglobin, requires 1.5 μL sample	www.alere.co.uk
	epoc®	Microfluidic card for the measurement of electrolytes and blood gas	
Alexeter Technol. LLC	RAID	Multi-strip assays for anthrax, ricin, bot tox, SEB, plague, tularemia, brucella, and pox	http://www.alexeter.com/biow/index.asp
Aline Inc.	Microfluidic slides, cuvettes	Design, development and manufacture of lab-on-a-chip and microfluidic products	www.alineinc.com
ANSYS	ANSYS CFD	Computational fluid dynamics software	www.ansys.com
Avalance Bioetch AB	Multifunctional pipette	Pneumatic control unit for localized delivered of small volumes to cells	www.avalancebiotech.com
Bartels Mikrotechnik GmbH	Microfluidic components: micropumps, check valves, tubing	Piezo actuated membrane micro pumps, fabricated in polymers: polyphenylsulfone, polypropylene	www.micro-components.com

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Table 1.1 (continued)

Company	Product	Description	Link
bi.Flow Systems GmbH	Flex,flow microscope slides	Microscope slides providing 6 liquid reservoirs with integrated micropumps which can be individually emptied in a controlled way	www.biflow-systems.com
Biomerieux-diagnostics	bioNexia rapid tests	Point-of-care rapid tests, take less than 10 min to perform. Used for diagnostics of HIV, malaria, hepatitis B, influenza, screening of bladder cancer, human cardiac Troponin I, C-reactive protein, human chorionic gonadotrophin	http://www.biomerieux.com/en/innovation/point-care#bioNexia® rapid tests
Biophysical tools	Microperfusion system MPS8	Microperfusion system for quantitative biomedical research and high throughput	www.biophysical-tools.de
Cellix	Kima	iPod touch microfluidic pump, 300 μL dead volume, flow rate: 15–35 mL/h	http://www.cellixltd.com/index.php/products/microfluidic-pumps/kima
	Vena8 Fluoro+	Biochip for rolling and adhesion assays on protein coatings, 8 channels/biochip, 0.8 μL volume of each channel	http://www.cellixltd.com/index.php/products/biochips/vena8-fluoro
Comsol	Comsol Multiphysics®—Microfluidics module	Tools for studying and simulate microfluidic devices including lab-on-a-chip, digital microfluidics, electrokinetic and magnetokinetic devices and inkjets.	www.comsol.com
CorSolutions	Microfluidic handling components: pumps, probes, stations	Simulation software for the predictive 3D modelling and simulation solutions for microfabrication and nanofabrication technologies	www.mycorsolutions.com
Coventor	MEMS+	Simulation software	www.coventor.com
Daktari Diagnostics	Daktari CD4	Portable electrochemical-base blood taste	www.daktaridx.com

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Table 1.1 (continued)

Company	Product	Description	Link
Diagnostics For All (DFA) (nonprofit organization)	Paper-based microfluidic platforms	Paper-based diagnostic portable platforms with results available in minutes. Used for detection of bovine heat, milk spoilage, aflatoxine, DNA and RNA sequences among others	www.dfa.org
Dolomite	Liquid handling micro components: chips, pumps, valves, connectors, sensors, interfaces	Used to build both simple and complex systems	www.dolomite-microfluidics.com
DST diagnostics	FastCheckPOC®	Microfluidic test-cassette for the qualitative identification of allergen-specific IgE; requires 15 μL samples, results after 30 min	www.dst-diagnostic.com
Elveflow	Microfluidic flow sensors	Monitor flow down to 1.2 nL/s with a resolution of 1.5 pL/s	www.elveflow.com
ESI	CFD-ACE+	Simulation software; it enables coupled simulations of fluid, thermal, chemical, biological, electrical, and mechanical phenomena	www.esi-cfd.com
	Open FOAM	Open source CFD toolbox	www.openfoam.com
Espira Inc.	Plastic microfluidic disk	Automated pathogen detection unit to purify DNA or RNA within 20 min	www.espirainc.com
FlowJEM	Plastic microfluidic components	Thermoplastic microfluidic devices fabricated in polycarbonate, PDMS, cyclic olefin and acrylic	www.flowjem.com
Fluidigm	Plastic microfluidic chips and kits	Nanoliter scale plastic chips for single-cell gene expression and single-cell mRNA sequencing workflow	www.fluidigm.com

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Table 1.1 (continued)

Company	Product	Description	Link
Fluigent	Fluidic handling components: microfluidic flow control systems, software		www.fluigent.com
Focus Diagnostics	3M™ Integrated Cycler	Real-time PCR instrumentation, can process up to 96 patient samples per run in less than 80 min. Lab on a disk type of device	http://www.focusdx.com/product-catalog/3m-integrated-cycler
GenMark Diagnostics	e-Sensor® cartridge	Plastic microfluidic cartridge for the mixing of target DNA with the signal probe solution for electrochemical detection	www.genmarkdx.com
GeneFluidics	Asklepios system	Disposable microfluidic cartridge for multiplex electrochemical detection, requires less than 500 μL sample volume	www.genefluidics.com
Hμrel Corp.	Hμrelflow™	Microfluidic cell-based assay platforms for organ-on-chip studies	http://hurelcorp.com/products-services/microfluidics
Klearia	LabInGlass® microreactors and sensors	Microfluidic chips fabricated in glass	www.klearia.com
LeukoDx	Accellix platform	Cartridge-based system to provide CD4/HIV monitoring and sepsis	www.leukodx.com
Life Technologies	TaqMan®	Real-time PCR assay, uses 384-well microfluidic cards, 1 μL reactions	www.lifetechnologies.com
LTF Technologies	Microfluidic and lab-on-a-chip components: microreactors, pumps, valves, starter set	Microreactors for the production of chemicals on-chip	www.ltf-gmbh.com
Medimate	Medimate Minilab	Lab-on-a-chip device for lithium and sodium detection in blood	www.medimate.com
microfluidic ChipShop	Fluidic platforms and interfaces, diagnostic platforms	Offers both catalogue products and costume-specific product developments for the developments of LOC and μTAS devices	http://www.microfluidic-chipshop.com

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Table 1.1 (continued)

Company	Product	Description	Link
Micronics (Sony Group Company)	PanNAT system	PCR system for diagnosis of infectious diseases, 100 μL volume sample, results for up to 3 pathogens in less than 1 h	http://www.micronics.net/products/diagnostic-products/PanNAT
	ABORhCard®	Provides ABO and Rh blood type from a finger stick blood sample in 2 min	http://www.micronics.net/products/diagnostic-products/immunohematology
	H-filter® Access™ card	Used for sample processing for analytical chemistry, rare reagent isolation and recovery	http://www.micronics.net/products/research-and-development
	H-filter® and T-sensor® Access™ card	Used to demonstrate the quantitative detection of an analyte in a sample using a control solution	
Micronit Microfluidics	Fluidic chips, microreactors, chip holders, microfluidic starter kit	Custom microfluidic products in glass and polymers	www.micronit.com
Nanomix	Omega 3 platform	Disposable multiplex-assay cartridge containing immunoassay-enzymatic test for critical cardiac diagnosis	www.nano.com
Numeca Int.	Fine™	CFD and multiphysics analysis and optimization software	www.numeca.com
Philips	Magnotech	POC biosensor platform using magnetic nanoparticles to measure target molecules in pL samples of saliva or blood	http://www.newscenter.philips.com/main/standard/news/backgrounders/2010/20100107_magnetic_biosensor.wpd#.U3rRstKSyuI
Radiometer	AQT90 Flex	Immunoassay analyzer, determine the level of an antigen in blood. Analyze up to 30 samples/h, results are obtained after 10 min	http://www.radiometer.com/en/products/immunoassay/aqt90-flex-analyzer
Roche	CoaguChek®	Self-monitoring coagulation status; requires 1 drop of blood and provide accurate results within 1 min	http://www.coaguchek.net

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Table 1.1 (continued)

Company	Product	Description	Link
Siloam Biosciences	Trova™	Optical detection, dry reagents, results in 15–20 min for cardiac Troponin-I detection	http://siloambio.com/lifescienceproducts/point_of_care_test_poct_platform/
SIMTech Microfluidics Foundry	Microfluidic chips, pumps and interfacing kits	Polymer base microfluidic components for biomedical applications	www.simtech.a-star.edu.sg
Sophion	Qpatch	Patch clamp system, it contains microfluidic channels for optimized liquid handling; up to 30.000 compounds tested per 24 h	www.sophion.com
Symscape	OpenFlow	Computational fluid dynamics software	www.symscape.com
Phadia (Thermo Scientific)	ImmunoCAP	Point-of-care microfluidic platform for the evaluation of patients with allergy-related symptoms. Results in 20 min as colored bands	http://www.phadia.com/en-GB/5/Products/ImmunoCAP-Rapid
thinXXS	Disposable microfluidic devices	Used in applications such as diagnostics, pharmaceutical, analytical, and medical industries	www.thinxxs.com
TearLab Corp.	TearLab Osmolarity System	Quantitative tests for diagnosing and managing dry eye patients. Use only 50 nL of tear film to diagnose	http://www.tearlab.com
Tetracore	RedLine Alert™	Immunochromatographic test based on capillary action for the in vitro qualitative identification of *Bacillus anthracias*	www.tetracore.com
Trianja Technol.	Glass microfluidic components:	Glass-based solutions for use in miniaturized biological and chemical devices	www.trianja.com
Trinean	Xpose	High-speed quantification of DNA, RNA, and proteins. Includes microfluidic carrier samples (capillary intake), 1–16 samples can be loaded and stay stable up to 2 h (no evaporation)	www.trinean.com

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Table 1.1 (continued)

Company	Product	Description	Link
μFluidix	Lab-on-a-chip platforms	Plastic platforms for handling of sub-microliter amount of liquid fabricated	www.ufluidix.com
Universal Biosensors	One Touch® Verio™	Blood glucose sensor; requires 0.5 μL sample, results within seconds	http://www.universalbiosensors.com/Products/Verio-Product-Information.aspx

Table 1.2 Sources of information about microfluidics and lab-on-a-chip

Name	Type	Editor	Comment	Link
Computers and fluids	Journal	Elsevier	Publish the development of numerical methods relevant to fluid flow computations, computational analysis of flow physics and fluid interactions	http://www.sciencedirect.com.globalproxy.cvt.dk/science/journal/00457930
Lab on a chip	Journal	Royal Society of Chemistry	Publish both fabrication and applications of LOC devices	http://www.rsc.org/publishing/journals/lc
Microfluidics and nanofluidics	Journal	Springer	Publish reports or research, techniques, and applications in microfluidics	http://link.springer.com/journal/10404
Optofluidics, microfluidics and nanofluidics	Journal	De Gruyter	Publish mostly applications of microfluidics	http://www.degruyter.com/view/j/optof
Analytical chemistry	Journal	ACS	Publish mostly applications of LOC devices	http://pubs.acs.org/journal/ancham
Biosensors and bioelectronics	Journal	Elsevier	Publish mostly applications of LOC with integrated sensors, e.g., electrochem., optical sensors	http://www.sciencedirect.com/science/journal/09565663
Microelectronic eng.	Journal	Elsevier	Publish mostly on techniques for fabrication of LOC devices	http://www.sciencedirect.com/science/journal/01679317
Biomedical microdevices	Journal	Springer	Publish research in the diagnostic and therapeutic applications of LOC devices	http://link.springer.com/journal/10544
Biomicrofluidics	Journal	American Institute of Physics	Publish on theory and applications of microfluidics	http://scitation.aip.org/content/aip/journal/bmf
Journal of Micromechanics and Microengineering	Journal	Institute Of Physics (IOP)	Publish on microfabrication of LOC devices	http://iopscience.iop.org/0960-1317/
Journal of Microelectromech. Systems	Journal	IEEE	Publish on the theory, modelling, design, fabrication, assembly, and packaging of LOC and microfluidic devices	http://eds.ieee.org/journal-of-microelectromechanical-systems.html

Chips and tips	Blog	RSC	Blog to exchange ideas and solutions on common practical problems encountered in the fabrication and use of LOC devices. Include videos	http://blogs.rsc.org/chipsandtips http://www.youtube.com/user/labonachipVideos#p/u
CFD online	Forum		Computational fluid dynamics software community. Provides news, forum, blogs, online tools, books guide, and discussions forums	www.cfd-online.com
Lab on a chip and microfluidics	Scientific community		Web site to formulate questions and suggest answers related to microfluidics and LOC devices	http://www.linkedin.com/groups/Lab-on-chip-Microfluidic-Devices-713657
Lab-on-a-chip and microfluidics	Scientific community	Technology Networks	Provides information about research news, business, products, conferences, courses, and jobs related to microfluidics and LOC devices	http://www.technologynetworks.com/LOAC
FluidicMEMS	Blog		Perspectives on LOC, microfluidic and bioMEMS technology	http://fluidicmems.com

Table 1.3 Conferences on microfluidics, lab-on-a-chip, and microTAS technology

Conference	Organizer	Topics	Link
Internat. conf. on miniaturized systems for chemistry and life sciences (μTAS)	The Chemical and Biological Microsystems Society	Premier forum for reporting research results in microfluidics, microfabrication, and applications of Loc and μTAS devices	http://www.microtas2014.org/, www.cbmsociety.org
Conference on microfluidic handling systems	Freiburg University	Discuss the latest results in the field of microfluidic handling systems (pumps, mixers, valves, sensors)	http://www.mfhs2014.uni-freiburg.de
European conf. on microfluidics		Design, fabrication and theory of LOC devices	http://microfluidics2014.eu
Point-of-care diagnostics World conference	Select Biosciences	Discuss the point-of-care diagnostics field	http://selectbiosciences.com/conferences/index.aspx?conf=POCDWC2014
Lab-on-a-chip European congress	Select Biosciences	Discuss innovative developments in LOC, microfluidics, and microarrays	http://selectbiosciences.com/conferences/index.aspx?conf=LOACEC2014
Lab-on-a-chip and microarray World congress	Select Biosciences	Discuss innovative developments in LOC, microfluidics, and microarrays	http://selectbiosciences.com/conferences/index.aspx?conf=LOACWC2014

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