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A Review on Recent Developments in Passive Plasma Separators Lab-on-Chip Microfluidics Devices

applied sciences

MDPI

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Presentation Outlines

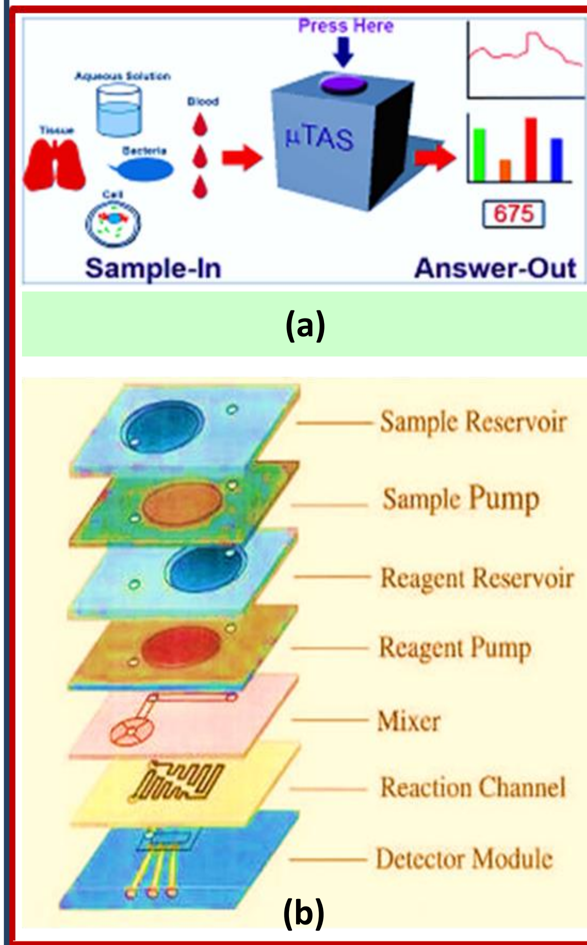
- Lab-On-Chip Devices
- Significance of Plasma Seaparation
- Microfluidics and Bioseparation
- Blood Component and Plasma Separation
- Literature Survey on the existing Plasma Separators
- References

Lab-On-Chip Devices

- Lab-On-Chip Devices (LOC) are also called as **(µ-TAS)** or are the miniaturized measurement devices.
- These systems aims to integrate several steps into a single, **automated device** or ‘chip’.

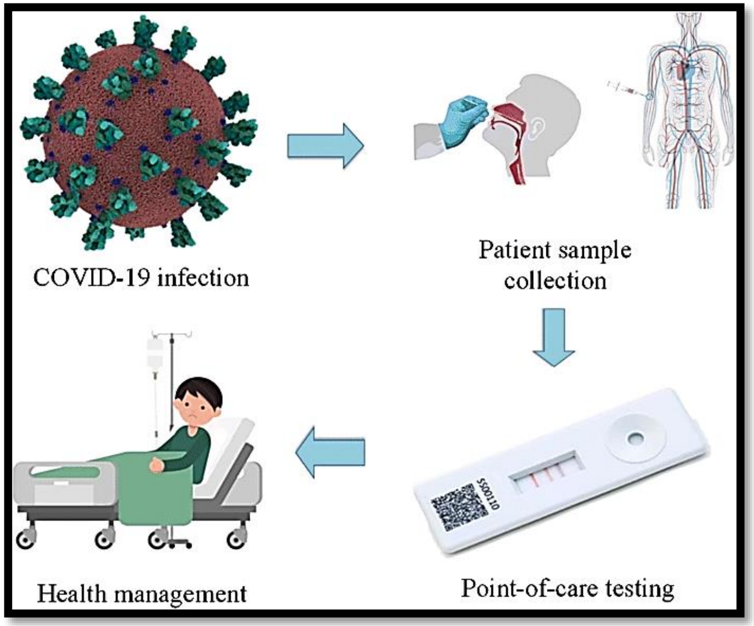
  1. Sample Collection
  2. Sample Preparation
  3. **Biomixing and Bioseparation**
  4. Sample Transfer for Analysis
  5. Detection and Results

- The LOC systems usually consist of two units
- ✓ A set of **microfabricated chambers and channels**,



Significance of Qualitative Rapid Biosensing

- Compatible to **Resource limited rural areas.**
- Prefered for **Rampant disease management.**
- **Mass detection and disease control** in Pandemic Situations like COVID-19.
- **Early detection** and control **at the very first acute stage of infection.**
- **POCT and faster health recovery**



Need of Plasma Separation

- Plasma contains all necessary **Proteins, RNAs, DNAs, Enzymes** facilitates testing through Biosensing Card Testing Platform
- Both **turn around time and accuracy** of diagnosis results are improved after RBCs and WBCs removal.
- **Plasma Testing** forms the bases of Biosensing Cards with **Greater Reliability**
- Plasma Samples are much **easier in handling and storage** as compared to whole blood sample
- Plasma itself rich in **anticoagulant Anti-Thrombin-III**, so it cannot be easily coagulated.

Microfluidics and Bioseparation

- Microfluidics is the scientific/engineering discipline underlying µ-TAS
- **Process or manipulate** small amounts of fluidics, i.e. 2-5ml, using channels measuring from tens to hundreds of micrometers.

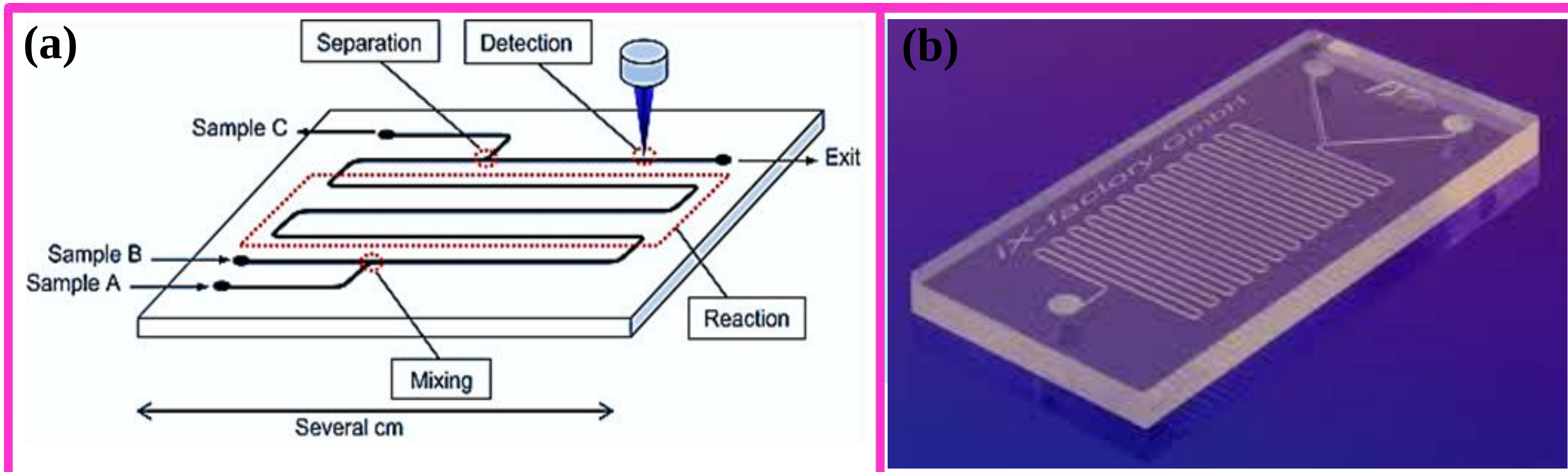
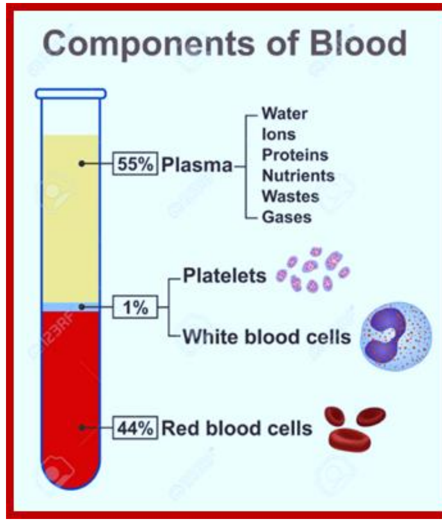
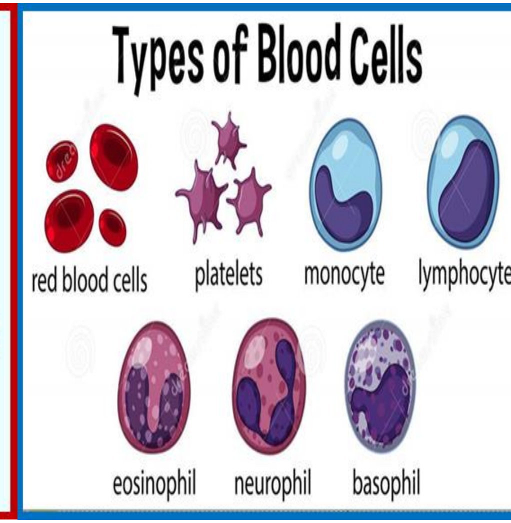


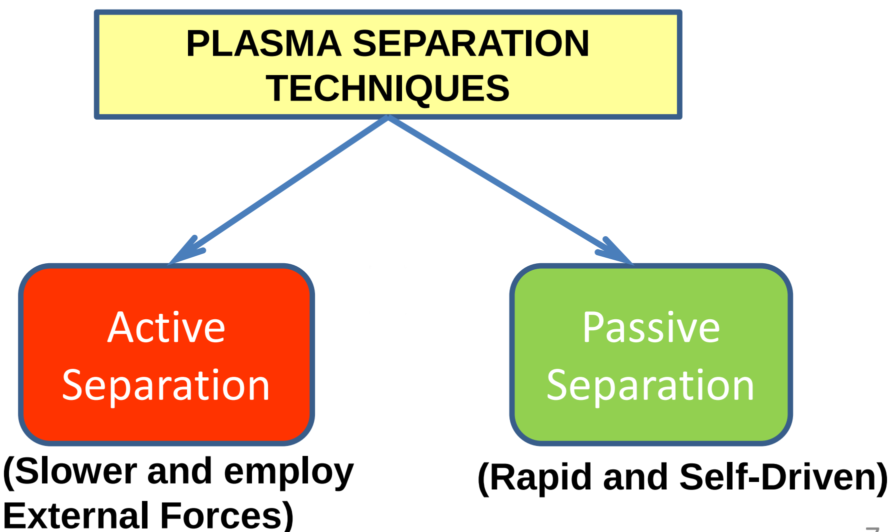
Fig. (a) Schematic Diagram of Microfluidics Lab-On-Chip Device; (b) Blue Print of Biomedical Chip

Blood Components and Plasma Separation Techniques

- **Active separation** methods exploit external forces and makes use of electrical, magnetic, dielectrophoretic, acoustics properties of blood cells.
- **Passive separation** methods employ internal rheology of blood components and simply use differences in cell properties for self-separation, such as the size, weight, shape, or stiffness.

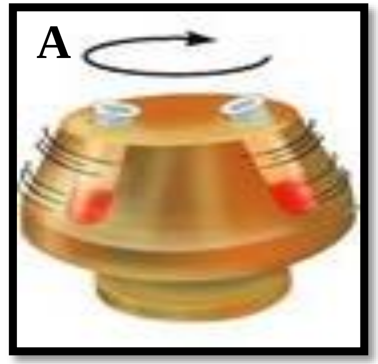


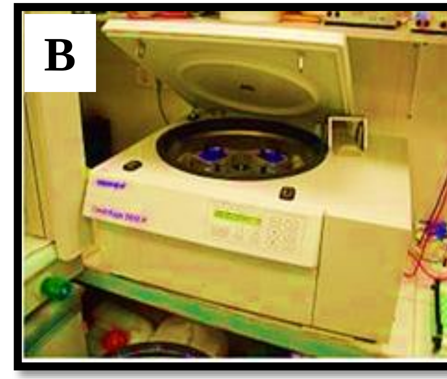




Active Plasma Separation

- ❑ Centrifuge-Tube Based (Fig. A)
- ❑ CD-based (Fig.B)





As described by Stokes' Law, the sedimentation rate of a particle, νr , due to centrifugal force is:

$$\boldsymbol{v_r = \frac{dr}{dt} = \frac{\left(\rho_{p\,-}\ \rho_m(r)\right).d^2\ .\ \mathbf{r}.\omega^2}{18.\eta_m\ (r)}}$$

and

$$rpm = \sqrt{\frac{RCF}{2.839\times10^{-5}.r}}$$

Where,

$\boldsymbol{\rho_p}$ is the particle density,

$\boldsymbol{\rho_m}$**(r)** is the media density at a given r,

d is the diameter of the particle,

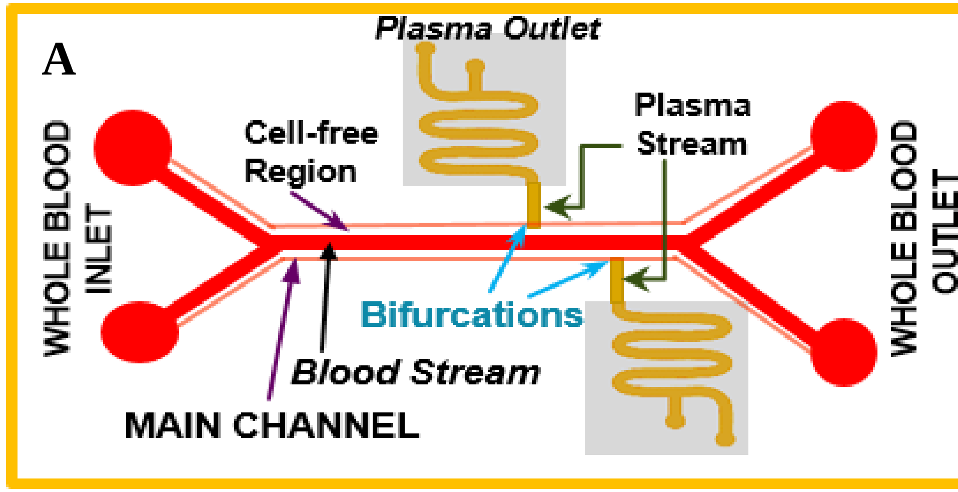
r is the radial distance from the rotation center,

ω is the angular velocity, $\boldsymbol{\eta_m}$**(r)** is the media viscosity at a given radius and **RCF** is relative centrifugal force.

Passive Plasma Separation

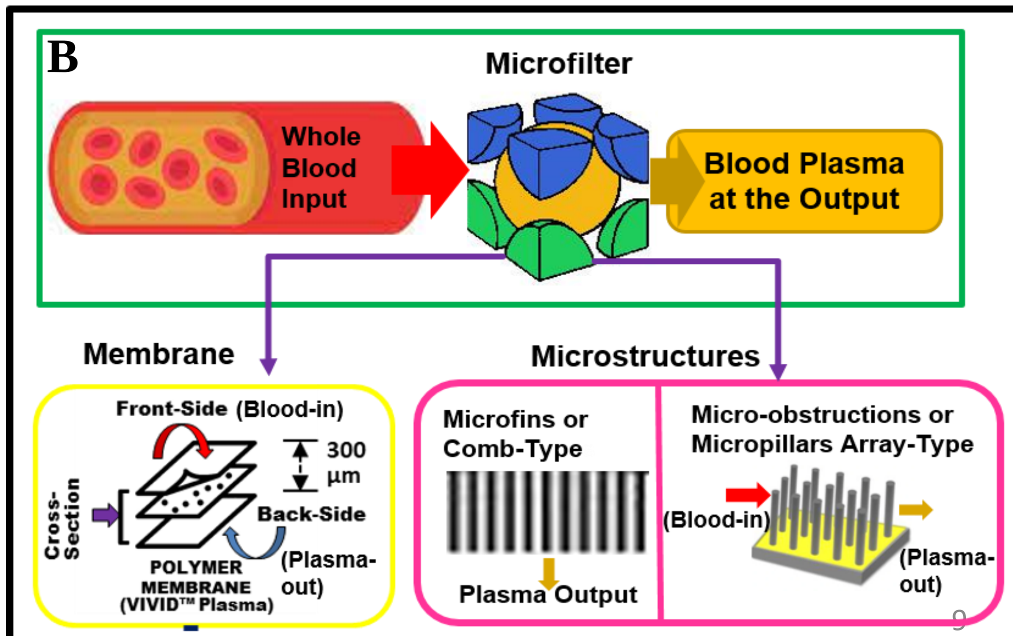
❑ **Microfluidics-based (Fig.A)**

Plasma follows ***bifurcations*** through Cell-Free Region due to Newtonian Behaviour.



❑ **Microfilters-based (Fig. B)**

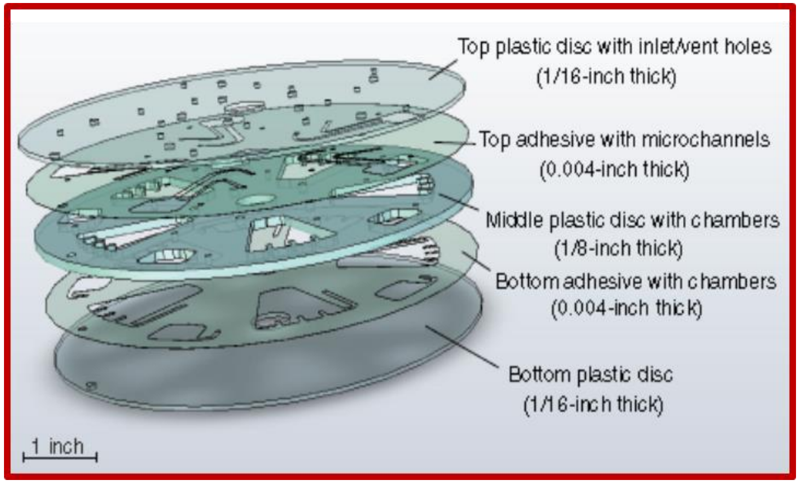
Microfilters are also preferred for ***size selection trapping*** and extraction of target particles.



Literature Survey on Plasma Separators

1. Active Devices based on Centrifugation

- ❑ Amasia and Madau et.al in **2010**, fabricated a **multilayer compact-disc centrifugal microfluidic device** using traditional **plastics machining techniques.**
- ❑ Moore et al. in **2011**, fabricated capillary valves in the centrifugal microfluidic disc by designing patterned surfaces, emphasizing on the **3D Printing Techniques.**



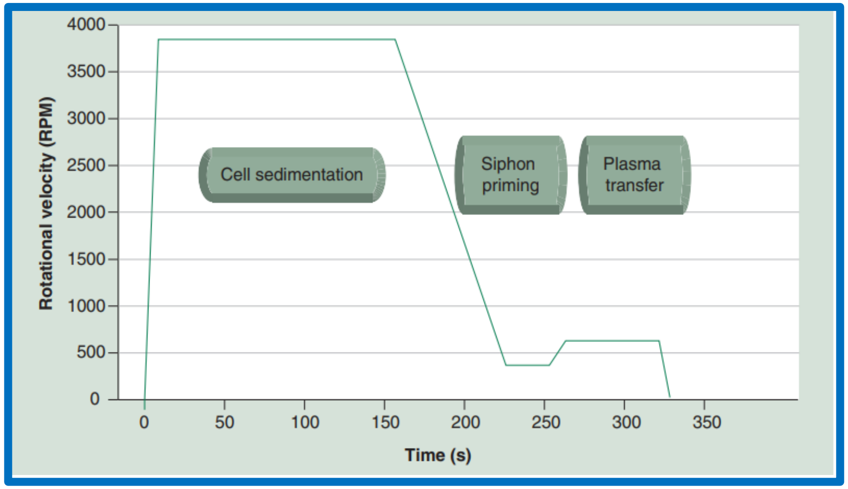
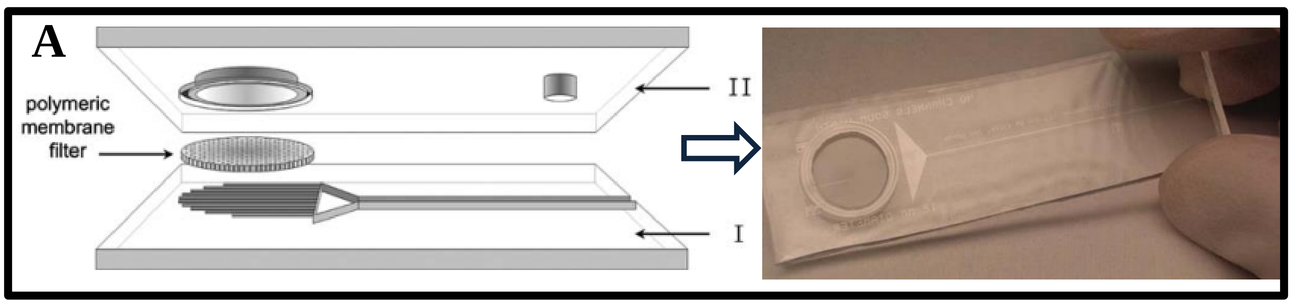


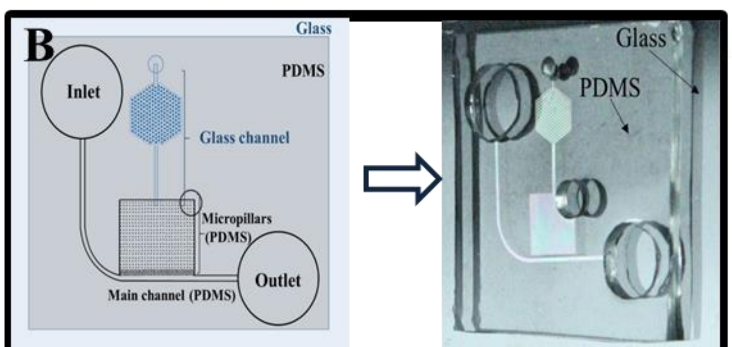
Fig. Device Structure and Spin profile graph detailing rotational velocity over time during the on-disc plasma separation process.

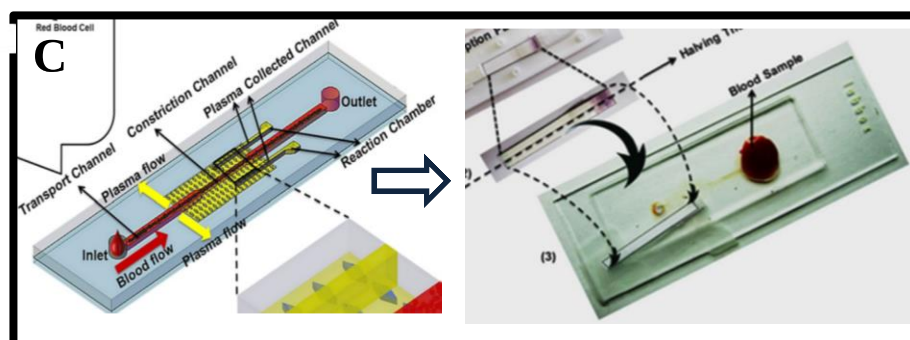
2. Passive Devices (Miniaturized On-Chip Separators) fabricated using various techniques

2.1. PDMS Soft Lithography

- Sara et.al **(2006)-** Separation Membrane-assisted Microfiltration and capillary force driven plasma extraction of high purity in lesser time (Fig. A)
- Park et.al **(2015)** – Retarded flow-assisted sedimentation, microfiltration and free-flow wetting of ethanol-treated collection channel (Fig. B)
- Madadi et.al **(2015) -** Separation Science, Fluid Dynamics, and Blood Rheology (Fig. C)





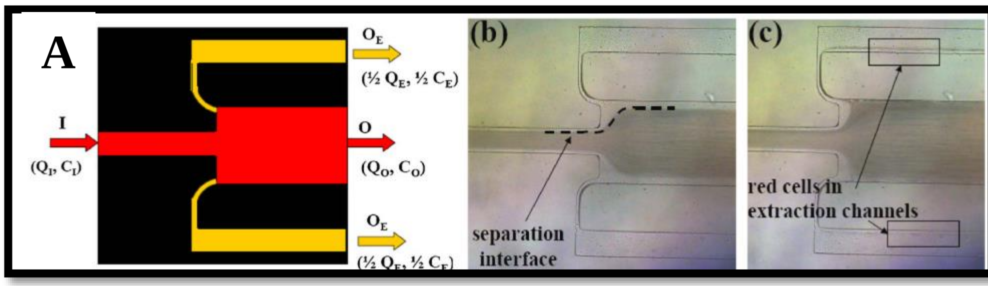


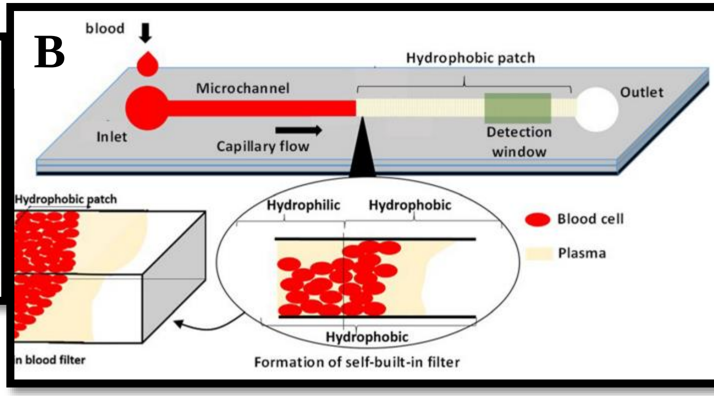
2. Passive Devices……contd.

2.2. Devices Fabricated Using Hybrid Technologies

Integration of Hybrid Chips fabricated using Standard Photolithigraphy and PDMS Soft-Lithography

- ❑ Sollier et.al **(2009) -** Innovative device is based on the lateral migration of red cells and the resulting cell-free layer, which is used to supply geometric singularities (an ear-cavity or a corner-edge) and locally enhanced clear plasma region (Fig. A)





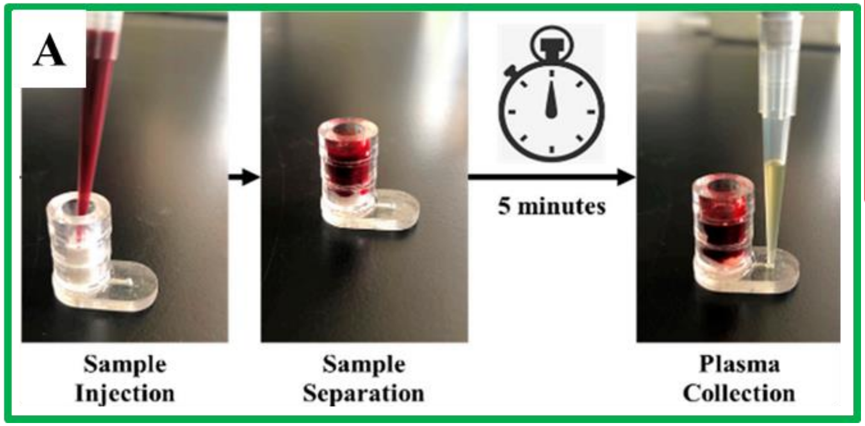
DLP 3D Printing, SU-8 Photolithography followed with PDMS Soft Lithography.

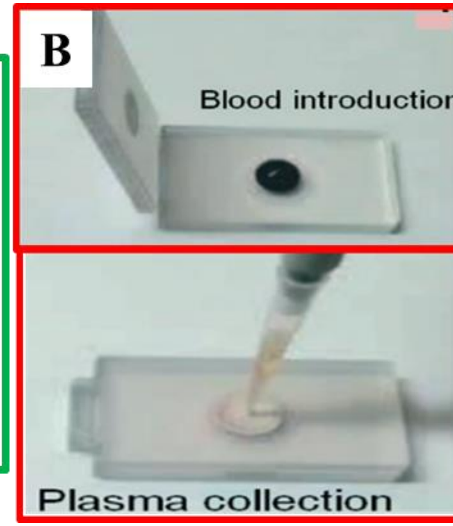
- ❑ Maria et.al **(2016) -** Capillary flow of blood in a microchannel with differential wetting, to induce a self- built-in filter for plasma separation and subsequent chromatographic detection of glucose (Fig. B)

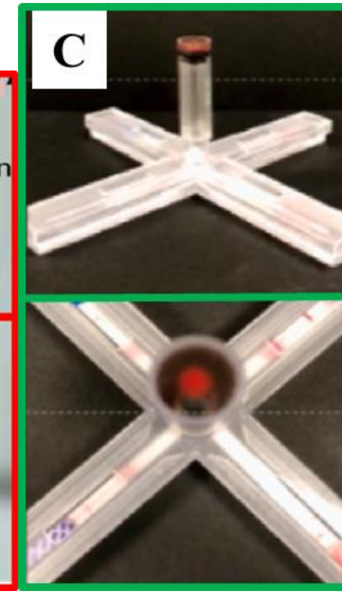
2. Passive Devices……contd.

2.3. CNC Micromachining

- Su et. al **(2020),** modular universal plasma-separation microdevice based on immunocapture and size filtering (Fig. A).







2.4. DLP 3D Printing

- Liu et. al **(2015)** introduces membrane based superhydrophobic clamshell style Plasma Separator. Gravitation assisted sedimentation and membrane-based filtration, while Superhydrophobic Surface-assisted Size extraction of plasma (Fig. B).

2.5. SLA 3D Printing

- Kim et. al **(2022)** – Glass fibre filter based erythrocyte binding, self-pressure driven plasma separation and multiple LFA diagnosis (Fig. C).

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REFERENCES

1. Civelekoglu, O.; Frazier, A.B.; Sarioglu, A.F. The Origins and the Current Applications of Microfluidics-Based Magnetic Cell Separation Technologies. *Magnetochemistry* **2022,** *8*, 10. https://doi.org/10.3390/magnetochemistry8010010
2. Garcia-Rey, S.; Nielsen, J.B.; Nordin, G.P.; Woolley, A.T.; Basabe-Desmonts, L.; Benito-Lopez, F. High-Resolution 3D Printing Fabrication of a Microfluidic Platform for Blood Plasma Separation. *Polymers* **2022**, *14*, 2537. https://doi.org/10.3390/polym14132537
3. Lopresti, F.; Keraite, I.; Ongaro, A.E.; Howarth, N.M.; La Carrubba, V.; Kersaudy-Kerhoas, M. Engineered Membranes for Residual Cell Trapping on Microfluidic Blood Plasma Separation Systems: A Comparison between Porous and Nanofibrous Membranes. *Membranes* **2021**, *11*, 680. https://doi.org/10.3390/membranes11090680
4. Hanbi Kim, Hyeonseek Park, Doo Ryeon Chung, Taekyung Kim, Eunkyoung Park, Minhee Kang, A self-pressure-driven blood plasma-separation device for point-of-care diagnostics. (2022) Talanta, 247, 123562 . https://doi.org/10.1016/j.talanta.2022.123562
5. Nair, K.P.P.R.; Veettil, T.C.P.; Wood, B.R.; Paul, D.; Alan, T. Haemoprocessor: A Portable Platform Using Rapid Acoustically Driven Plasma Separation Validated by Infrared Spectroscopy for Point-of-Care Diagnostics. *Biosensors* **2022**, *12*, 119. https://doi.org/10.3390/bios12020119
6. Eke, C. S., Jammeh, E., Li, X., Carroll, C., Pearson, S., & Ifeachor, E. **(2021**). Early Detection of Alzheimer's Disease with Blood Plasma Proteins Using Support Vector Machines. *IEEE journal of biomedical and health informatics*, *25*(1), 218–226. https://doi.org/10.1109/JBHI.2020.2984355
7. Wang, Y.; Nunna, B.B.; Talukder, N.; Etienne, E.E.; Lee, E.S. Blood Plasma Self-Separation Technologies during the Self-Driven Flow in Microfluidic Platforms. Bioengineering **2021,** 8, 94. https://doi.org/10.3390/bioengineering80700
8. Su, X., Zhang, J., Zhang, D., Wang, Y., Chen, M., Weng, Z., Wang, J., Zeng, J., Zhang, Y., Zhang, S., Ge, S., Zhang, J., & Xia, N. (2020). High-Efficiency Plasma Separator Based on Immunocapture and Filtration. *Micromachines*, *11*(4), 352. https://doi.org/10.3390/mi11040352
9. Jørgensen, M. K., Eriksen, K. B., & Christensen, M. L. **(2020).** Particle Track and Trace during Membrane Filtration by Direct Observation with a High Speed Camera. *Membranes*, *10*(4), 68. https://doi.org/10.3390/membranes10040068
10. Yasukawa, T.; Yamada, J.; et.al. Microfluidic Separation of Blood Cells Based on the Negative Dielectrophoresis Operated by Three Dimensional Microband Electrodes. *Micromachines* **2020,** *11*, 833. https://doi.org/10.3390/mi11090833
11. Mateen, S.A., Bhole, K.S. A review on microfluidic devices for separation of blood constituents. ICEMEM-2019. IOP Conf. Series: Materials Science and Engineering 810 **(2020)** 012024. http://dx.doi.org/10.1088/1757-899X/810/1/012024
12. Wang, Y., Keller, K., & Cheng, X. **(2019).** Tangential Flow Microfiltration for Viral Separation and Concentration. *Micromachines*, *10*(5), 320. https://doi.org/10.3390/mi10050320
13. Wei Chien, Zunmin Zhang, Gerhard Gompper, and Dmitry A. Fedosov , "Deformation and dynamics of erythrocytes govern their traversal through microfluidic devices with a deterministic lateral displacement architecture", Biomicrofluidics 13, 044106 (2019) https://doi.org/10.1063/1.5112033
14. Rhee MK, Ho Y-L, Raghavan S, Vassy JL, Cho K, Gagnon D, et al. **(2019)** Random plasma glucose predicts the diagnosis of diabetes. PLoS ONE 14(7): e0219964. https://doi.org/10.1371/journal.pone.0219964
15. Benjamin, R. J., & McLaughlin, L. S. (2012). Plasma components: properties, differences, and uses. *Transfusion*, *52 Suppl 1*, 9S–19S. https://doi.org/10.1111/j.1537-2995.2012.03622.x
16. Nader, E. Blood Rheology: Key Parameters, Impact on Blood Flow, Role in Sickle Cell Disease and Effects of Exercise. Front. Physiol., 17 October **2019**. Sec. Red Blood Cell Physiology. https://doi.org/10.3389/fphys.2019.01329
17. Raiza, N. Kazi. Early detection of kidney function in diabetic kidney disease: An approach to prevent end stage renal disease Journal of Interventional Nephrology **(2018)** 1(1), 15–18
18. Faustino, V.; Catarino, S.O.; Pinho, D.; Lima, R.A.; Minas, G. A Passive Microfluidic Device Based on Crossflow Filtration for Cell Separation Measurements: A Spectrophotometric Characterization. *Biosensors* **2018**, *8*, 125. https://doi.org/10.3390/bios8040125

REFERENCES…contd.

19. Rafeie, M., Zhang, J., Asadnia, M., Lib. W., and Warkiani, M. E. Multiplexing slanted spiral microchannels for ultra-fast blood plasma separation. **(2016)** Lab on a Chip, 16(15), 2791–2802. https://doi.org/10.1039/C6LC00713A
20. Maria, M. S., Rakesh, P. E., Chandra, T. S., & Sen, A. K. **(2016).** Capillary flow of blood in a microchannel with differential wetting for blood plasma separation and on-chip glucose detection. *Biomicrofluidics*, *10*(5), 054108. https://doi.org/10.1063/1.4962874
21. Namgung, B.; Tan, J.K.S.; Wong, P.A.; Park, S.-Y.; Leo, H.L.; Kim, S. Biomimetic Precapillary Flow Patterns for Enhancing Blood Plasma Separation: A Preliminary Study. *Sensors* **2016**, *16*, 1543. https://doi.org/10.3390/s16091543
22. Park, S., Shabani, R., Schumacher, M. *et al.* On-chip whole blood plasma separator based on microfiltration, sedimentation and wetting contrast. *Microsyst Technol* **22**, 2077–2085 **(2016).** https://doi.org/10.1007/s00542-015-2656-7
23. Madadi, H., Casals-Terré, J., & Mohammadi, M. **(2015).** Self-driven filter-based blood plasma separator microfluidic chip for point-of-care testing. *Biofabrication*, *7*(2), 025007. https://doi.org/10.1088/1758-5090/7/2/025007
24. Schwarzenbach, H., Hoon, D. S., & Pantel, K. **(2011).** Cell-free nucleic acids as biomarkers in cancer patients. *Nature reviews. Cancer*, *11*(6), 426–437. https://doi.org/10.1038/nrc3066
25. Moore, J.L., McCuiston, A., Mittendorf, I. et al. Behavior of capillary valves in centrifugal microfluidic devices prepared by three-dimensional printing. Microfluid Nanofluid 10, 877–888 **(2011).** https://doi.org/10.1007/s10404-010-0721-1
26. Wagner, J. **(2012).** Free DNA--new potential analyte in clinical laboratory diagnostics?. *Biochemia medica*, *22*(1), 24–38. https://doi.org/10.11613/bm.2012.004
27. Zhang, X. B., Wu, Z. Q., Wang, K., Zhu, J., Xu, J. J., Xia, X. H., & Chen, H. Y. **(2012).** Gravitational sedimentation induced blood delamination for continuous plasma separation on a microfluidics chip. *Analytical chemistry*, *84*(8), 3780–3786. https://doi.org/10.1021/ac3003616
28. Franklin, B. S., Vitorino, B. L.,et.al. **(2011).** Plasma circulating nucleic acids levels increase according to the morbidity of Plasmodium vivax malaria. *PloS one*, *6*(5), e19842. https://doi.org/10.1371/journal.pone.0019842
29. Amasia, M., Madau, M. Large-volume centrifugal microfluidic device for blood plasma separation. October **2010** Bioanalysis 2(10):1701-10. https://doi.org/10.4155/bio.10.140
30. Rodriguez-Villarreal A I, Arundell M, Carmona M and Samitier J High flow rate microfluidic device for blood plasma separation using a range of temperatures, **2010.** Lab Chip 10 211-19. https://doi.org/10.1039/B904531G
31. Zheng, S.; Lin, H.; Liu, J.-Q.; Balic, M.; Datar, R.; Cote, R.J.; Tai, Y.-C. Membrane microfilter device for selective capture, electrolysis and genomic analysis of human circulating tumor cells. J. Chromatogr. A **2007**, 1162, 154–161
32. Rainer, T. H., Wong, L. K., Lam, W., Yuen, E., Lam, N. Y., Metreweli, C., & Lo, Y. M. **(2003).** Prognostic use of circulating plasma nucleic acid concentrations in patients with acute stroke. *Clinical chemistry*, *49*(4), 562–569. https://doi.org/10.1373/49.4.562
33. Moorthy and D.J. Beebe, In situ fabricated porous filters for microsystems. Lab Chip 3, 62 **(2003).** https://doi.org/10.1039/B300450C
34. H. Andersson, W. van der Wijngaart, P. Enoksson, and G. Stemme, Micromachined flow-through filter-chamber for chemical reactions on beads. Sensors and Actuators B-Chemical 67, **203** **(2000).**
35. Kalmokoff, M.L., Koval, S.F. & Jarrell, K.F. Relatedness of the flagellins from methanogens. *Arch. Microbiol.* **157**, 481–487 **(1992).** https://doi.org/10.1007/BF00276766
36. Cripps, CM. Rapid method for the estimation of plasma haemoglobin levels. Journal of Clinical Pathology **1968;** 21:110-112.

THANK YOU!!