International Journal of Innovative Technology and Exploring Engineering (IJITEE)
ISSN: 2278-3075 (Online), Volume-9 Issue-8, June 2020

Impedance Cytometry for Detection of Particle and Counting using Low Phase Noise DDFS – LUT

G. Ramana Reddy, P. Chitra, K. Prakash

***Abstract:** The biotechnology is widely growing with many technologies, still we see a large gap in real-time implementation of complete blood counting. To increase the resolution and accuracy of the measurements advanced communication DDFS can be used. The elements in Direct Digital Frequency Synthesizers (DDFS) involved are: phase accumulator, a phase to amplitude converter which also called look up table (LUT), a digital to analog converter along with active filter. Direct digital frequency synthesis is a method for generating complex high - frequency waveforms for specific applications. This DDFS generates frequency resolution which makes it ideal components use in radar system, software defined radio, modern wireless communicating system, advanced satellite navigation purpose. Use cases for high frequency we get interrupt with spurious noise, larger ROM size, and high power consumption of DDFS signal. In this paper we are proposing the use of signal generated from DDFS to impedance cytometry in which the number of particles gets detected by getting the output frequency different from the input frequency. Due to use of small frequency range of signal spurious noise, power consumption and ROM size will be less with effective performance.*

***Keywords:** Direct Digital Frequency Synthesizers (DDFS), Digital to Analog Convertor (DAC), Read Only Memory (ROM), Flow Cytometry, Cell analysis and Signal Conditioning.*

I. INTRODUCTION

Theoretical research has been done on advanced waveforms with unique characteristics. Advanced waveforms generated have practical applications several areas like in modern communication. In this paper we are trying to relate it to biological field. Significant Advantages of a DDFS are that its phase, amplitude and output frequency can be absolutely and quickly controlled under digital processor control.

- For converting phase information from phase accumulator to amplitude we require larger ROM size but by increasing ROM size power consumption and access time increases. Reducing ROM size with spectral performance enhancing some offers, linear interpolation method [1].

Revised Manuscript Received on June 30, 2020.
* Correspondence Author
Prakash Kodali*, Department of ECE, National Institute of Technology, Warangal, India. Email: kprakash@niw.ac.in
G. Ramana Reddy, Research Scholar, Department of ECE, Sathyabama Institute of Science and Technology, Chennai, India. Email: gujjula.ramanareddy@gmail.com
P. Chitra, Professor, Department of ECE, Sathyabama Institute of Science and Technology, Chennai, India. Email: chitra.ece@sathyabama.ac

- The use commonly available architectures rapidly increased, with frequency limitation by low speed fabricated devices to generate a high frequency signal wideband data streams [2].
- A DDFS with a 32 bit ROM of 2 GHz using 0.13 µm CMOS technology for signal gets increasing the operating speed in many applications. To improve the efficiency the power hungry amplitude converted from phase method is removed and linear digital signal to analog signal is replaced by nonlinear DAC challenge [3].
- 2 GHz DDFS based on LUT and rotation is capable of increasing speed and resolution. This proposed method has high clock frequency supports with the conventional PAC by replacing 7 pipelined rotational units [4] for better storage of signal generation. Approximation and multiplier technology used to reduce the LUT's in from high frequency signal generation.
- DDFS without a ROM was introduced and it reduced much power, area and speed problem in several cases. That reduces the large ROM table usage in signal generation storage. More than 3 polynomials utilize to not using ROM table and had a phase to signal mapping [5].
- Hybrid frequency synthesizers operate over wide frequency range and due to use of copies of fundamental frequency noise performance is reduced. The use of images increases output frequency [6].
- Design of a k band fast hopping synthesizers based on DDS and PLL is designed for a frequency modulation continuous wave radar system. 50 MHz step frequency provided and the lock time considered below 150ns [7].
- Fractional frequency synthesis terra hertz range instrument which will compares the spurious level, power consumption, noise level [8].

For the particle identification, perfect signal has to be generating from the DDFS and then applied to sensor electrodes. To get high throughput and better accuracy the impedance cytometry is an emerging resonance field. Impendency to data analysis will be very useful to the electric/dielectric properties of cells and its other parameters. Coulter counter has FAC's (Fluorescence Activated Cell) sorting or basic methods widely used for high throughput cell counting and classification. Coulter counting device works with AC and DC change of units, at low frequencies it identifies properties of cells during the cell passing through sensor region.

AC components can provide cell dimensions, shapes and quantity [9]. In bio-related studies coulter counter and fluorescence - activated cell sorting (FACS) are widely used as high throughput cell counting and classification methods from the initial stage. Coulter counter detects a change of field in direct current or low frequency alternating current impedance signal caused by particle or cell passing through the detection region, which can give us information about particle size [10]. This paper is arranged as follows. Section 2 gives the overall system architecture of the proposed DDFS. Section 3 gives us an Overview of Impedance based micro fluidic Cytometry. Electrode Design, working of Cytometry is explained in section 4 and 5.

II. BASIC STUDY OF DDFS

The phase accumulation block is increased by digital notation to the analog signal generation, using the fundamental element like phase accumulator using FCW input at every clock cycle.

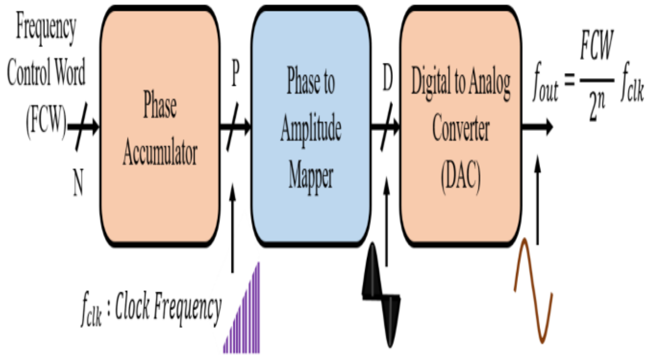

Fig.1. Basic Architecture of DDFS.

The phase information is converted to amplitude information by phase to amplitude convertor and then by using D/A convertor digital signal get converted into analog signal. Overall block architecture view with fundamental elements of DDFS is shown in figure 1.

We gave two input FCW & clock reference to phase accumulator and phase accumulation integrate the value of FCW at each clock duration and generated output frequency is given by-

$$f_{out} = {f_{clk} * \text{FCW}}/{2^N}$$

Modulo - 2^N saw tooth waveform will be generated at the output of phase accumulator when DDFS gets clocked, here N corresponding to number of bits carried-out in phase accumulator. The signal followed with the conversion to a sampled sinusoid by phase to amplitude converter (PAC). The simplest approach for phase-to-sinusoid amplitude is implemented as a ROM LUT. To transfer the whole bit of accumulator to LUT the memory and power consumption will be more so we allow only M number of bits out of N number of bits to the PAC. This effect is known as truncation effect which creates phase noise. So, we use a method which requires smaller ROM size for fast responses. The phase increment word FCW is an integer, therefore the frequency resolution is found by setting ΔFCW = 1;

It is equal to –

$$\Delta f = {f_{clk}}/{2^N}$$

III. CONCEPT OF IMPEDANCE CYTOMETRY

3D electrodes base Impedance Cytometry is a technique which uses to measure several parameters of the particles. An externally applied alternating electric field from the DDFS – DAC is used to probe the particles at certain frequency. These can be achieved by applying potential between input and output pair of electrode resulting current measured through the system. The impedance is the ratio of the voltage to current passing through the system to evaluate the size of particles. The development of micro fluidics and lab-on-a-chip type devices with high-end fabrication technique has allowed single cell pass through to be performed for high sensitivity and high throughput. Counting methods using impedance measurement for single cell analysis are Coulter Counting, Its block representation overview shown in figure 2. Impendency to will be an accumulation and well established model for counting different types of cells. Multiple frequency ranges can be adopted at lower values and system will attain good sensitivity with less noise. They represent a well-established method for counting particles. The primary distinction from the coulter principle is that we are measuring with AC (alternating current) over a broad frequency range, while coulter works with direct current or with AC at exceptionally selected low frequencies.

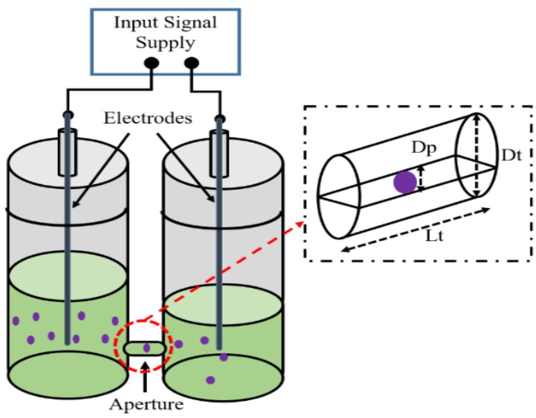

Fig.2. Illustrating the working principle of coulter counters.

IV. ELECTRODE DESIGN

Three common configurations used in impedance cytometry are side by side electrodes, parallel electrodes and constriction electrodes.

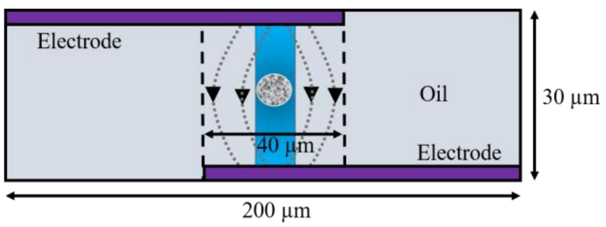

Fig.3. Electric field effect when particle is in the channel

Every design connection is based on similar detection method when particle flows between a pair of electrode the electric field between the electrodes get disrupted and the current measure across the electrode will change. In coplanar electrode the fabrication process is easy as single alignment is needed to guide electrodes to the necessary position inside the channel. Electric field across coplanar electrode structure is non- uniform, the impedance measurement relied on the perpendicular position of the particle in the detection area. To generate homogenous electric field it is placed at the bottom of lateral channel perpendicular to the main channel. The coplanar electrodes have poorer sensitivity and also fringing effect will introduce due to lateral channel. A pair of electrode is used in parallel electrode design. It has better sensitivity as electric field distribution is less divergent. In parallel electrode design fabrication process is complex, as two alignment steps are needed to align the top and bottom electrode configuration. It is also having vertically position dependency; parallel electrode structure is shown in figure 3. Because of absence of direct contact between the electrode and particle the current leakage may occur in which current may pass through high conductivity fluid. Either coated, deposited or 3D printed AgCl electrodes used to reduce the environment causes/effects with counting cells.

V. CYTOMETRY INTERFCING

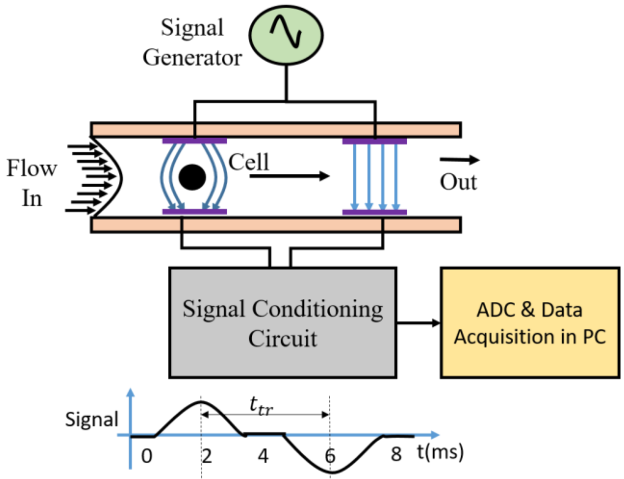

Fig.4. Electrodes 3D arrangement and electronics interface of an Impedance Flow Cytometry.

Electric field exist in the sensor, the polarization of the particles occur due to the charge accumulation at the limits between the aqueous medium and the plasma membrane of the particles as an alternating current is applied. Flow cytometry is used to found number of particles using coulter counter. Once the sample has been prepared for flow cytometry analysis, the prepared sample is fed into flow cytometry instrument. A flow cytometry contains several key components including the sample, fluidic that move the sample into the flow Cytometry, electrode to which voltage signal is given, detector to sense the change in signal and a computer system to get output data into form that can be analyzed by the researcher. The overall processing of particle counting is depicted in figure 4.

When there is no particle in the channel then detector or sensor sense the input signal without distortion as there is no change in the electric field. i.e. output follows the input signal without any change in magnitude and frequency. If there is a particle in the channel then the electric field get distorted and the detector will detect signal different from applied input signal. We apply alternating voltage to the electrode throughout the experiment process.

VI. HARDWARE IMPLEMENTATION & RESULTS

HARDWARE: The signal can be generated using a FPGA module and it can be transmitted through a transmitter to electrodes channel. The same generated signal can be given or taken to the reference in the controller system to compare the detected signal after the process of particle flow in a channel. The implementation is hardware and software related to connecting the real time sample/particle to the system.

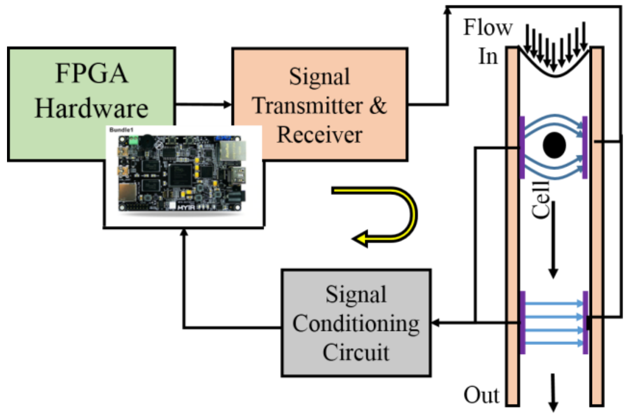

Fig.5. Block level representation of overall proposed system model.

This a novel proposal of using DDFS in bio application, we are not showcasing the hardware and results related to particle. Different models of embedded concepts have been developed but, nobody has implemented this concept in the area of biomedical applications with advanced signal processing model hardware. In the future work we show the developed hardware part with detailed results relation to particles counting. The block diagram model is shown in below figure 5, overall cycle of the system operation.

RESULTS: Passing beads through the 3D electrode sensor with a particular flow rate and applied alternating electric field which was generated from hardware module.

When the particle is flowing through channel the 1st set of electrodes feel the change in electric field and that is compared with the other 2nd set of reference electrode. The cumulated data is shown in below figure 6 (a) and (b). Beads size of the 15 µm are flowed through channel and applied voltage is 1 VPP at 500 KHz frequency.

The resultant signal will be few millivolts, the figure depicts with particle and without particle flow data. In the provided figure 6 the x-axis indicates the time (ms) duration of the signal recording and y-axis show the response in few millivolts (mv). Using the other image processing technique or data processing the number of particles can be counted and quantified w.r.t sample flow rate and time stamps.

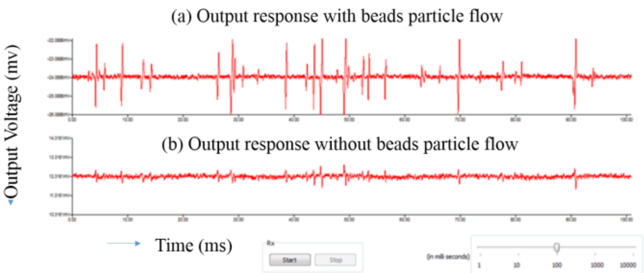

Fig.6. Output response with sample and without sample beads. (a) With particles (b). Without particles.

VII. CONCLUSION

Direct Digital Frequency Synthesizer is found that signal generation at high frequencies will be effectively used for biomedical applications. We get to know how to reduce the phase noise, power consumption and spurious level of signal for the best use and extraction of signal at high quality. High resolution frequency, wide band, high frequency output from the DDFS are easily used and analyzed. Generally we see the application of DDFS on radar communication, satellite communication so; we relate it to the biological world for better results with good and analysis. Based on literature survey we are relating DDFS in Impedance Cytometry to count the number of particle passing through the channel were observed. In the DDFS based impedance cytometry the signal fed to the sensor and resultant signal has be trapped out with the supplied reference signal cancelation so, the particle signal was detected. The resultant signal can be proceed further using image processing or data analysis we can quantify number of particle.

REFERENCES

1. S. Khilar, K. Parmar, S. Saumi, and K. Dasgupta, "Design and analysis of direct digital frequency synthesizer," *2008 First International Conference on Emerging Trends in Engineering and Technology*, pp. 1302-1306, 2008.
2. B. C. Rutherford and C. S. Lewis, "Practical direct digital synthesis for realizing high frequency signals from low frequency domains," in *2018 IEEE Radar Conference (RadarConf18)*, 2018: IEEE, pp. 0670-0675.
3. X. Guo, D. Wu, L. Zhou, H. Liu, J. Wu, and X. Liu, "A 2-GHz 32-bit ROM-based direct-digital frequency synthesizer in 0.13 µm CMOS," *Analog Integrated Circuits and Signal Processing*, vol. 94, no. 1, pp. 127-138, 2018.
4. Y. Yang *et al.*, "A 2-GHz direct digital frequency synthesizer based on LUT and rotation," in *2018 IEEE International Symposium on Circuits and Systems (ISCAS)*, 2018: IEEE, pp. 1-5.
5. T.-Y. Tsai, H.-Y. Shih, and C.-C. Wangt, "A pipeline ROM-less DDFS using equal-division interpolation," in *2017 International SoC Design Conference (ISOCC)*, 2017: IEEE, pp. 19-20.
6. V. Romashov, L. Romashova, K. Khramov, K. Yakimenko, and A. Doktorov, "Wide-band hybrid frequency synthesizer with improved noise performance," in *2018 Moscow Workshop on Electronic and Networking Technologies (MWENT)*, 2018: IEEE, pp. 1-4.
7. Z. Hu and G. Sun, "Design of a K-band fast hopping frequency synthesizer," in *2017 2nd IEEE International Conference on Integrated Circuits and Microsystems (ICICM)*, 2017: IEEE, pp. 137-140.
8. A. Tang *et al.*, "DDFS and ΣΔ approaches for fractional frequency synthesis in terahertz instruments," *IEEE Transactions on Terahertz Science and Technology*, vol. 8, no. 4, pp. 410-417, 2018.
9. W. R. Hogg and W. H. Coulter, "Apparatus and method for measuring a dividing particle size of a particulate system," ed: Google Patents, 1971.
10. P. Walker, K. Woodyer, and J. Hutka, "Particle-size measurements by Coulter Counter of very small deposits and low suspended sediment concentrations in streams," *Journal of Sedimentary Research*, vol. 44, no. 3, pp. 673-679, 1974.

AUTHORS PROFILE

Mr. G. Ramana Reddy, Research Scholar in Department of ECE, Sathyabama Institute of Science and Technology (Deemed to be University), He completed his master's program M .Tech from HITS Engineering College at Hyderabad. He is working in Nalanda Institute of Engineering and Technology (NIET group in Guntur Dt.,) as associate professor with 8 years of teaching experience. He has more than 10 journals and conference papers. He is experienced in teaching various courses in under graduation and post-graduation programs. He owned the life time membership in society and associations like ISRD and IAENG. He has been into many government funded activities like MSME. FDP and Ratified (JNTU-K) programs with certificate.

Dr P. Chitra, Professor, Department of Electronics and Communication Engineering, Sathyabama Institute of Science and Technology (Deemed to be University). She had received her doctorate in Sathyabama University in September, 2014, she had more than 17 years of teaching experience home institute, other prestigious universities. She taught variety of courses for post-graduation program and Under Graduation program levels. Her research area has widespread like Very Large Scale Integrated Circuits (VLSI), Signal Processing, and Embedded Systems in wide applications. She published more than 25 papers in reputed international , national journals and international conferences. She participated in various department activities, has good experience in various in-charge duties. Resource person and participant in various faculty development programs in home institute and outside the institutes.

Dr. Prakash Kodali, Ph.d, M.Tech from Indian Institute of Science (IISc), Bangalore. His research interests are socially relevant and technology transfer based on Bioelectromechatronics area. Core research in flexible electronics and embedded systems. He is working as assistant professor in NIT Warangal, Department of E.C.E. Research experience in various institute, Startup and companies for 8 years. He is a technical advisor in Microxlabs, Reinvlabs in Bangalore and Hyderabad. He got many awards and rewards form prestigious universities and societies. He is an IETE, IEEE member and published more than15 papers in various journals and conferences. One Indian patent got published and 3 more patents filed as full and partial in 2019 on various aspects of research. He conducted various faculty development programs and participant in different areas having learning thrust in new trends.