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Hand-Powered Centrifugal Platform for Fast Plasma-Based Diagnostics

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Abstract: Detection of specific biomarkers in blood plasma is essential for fast and accurate diagnosis and treatment of medical conditions. Hand-powered centrifuges offer a promising alternative to conventional centrifuges for blood seperation in resource-limited settings. Though these systems are efficient for blood plasma extraction, the necessary steps for performing the analysis remain. In this paper a concept for automatic combining of a detection reagent with blood plasma during hand-powered centrifugation is presented. Evaluation showed the successful routing of a reagent carrier to a defined position after the designed number of centriufagtion cycles. Furthermore it could be shown, that even with varying applied force (exceeding a minimum value) the extracted plasma volume is sufficient when combining with the reagent. The system reached a maximum rotational velocity of up to 9000 rpm which has proved to be equivalent to about 4500 rpm on a conventional centrifuge.

Keywords: hand-powered centrifuge, blood separation, plasmabased point-of-care, automatic blood plasma reagent combining.

1 Introduction

Fast and accurate diagnosis of time-critical medical conditions are important for the treatment of many illnesses. Diagnosis requires the detection of a specific biomarker in human blood. The presence of blood cells can affect test results, so the analysis of blood plasma has become necessary for biomarker analysis [1]. The most widely used way to extract blood plasma from whole blood is via centrifugation. Though centrifuges are efficient, they are expensive, need electrical power, and are generally not portable. Beyond that, trained operators are required for the necessary steps in the analysis procedure. Thus, biomarker analysis in blood plasma is a challenge in resource-limited settings.

Hand-powered centrifuges are a low-cost solution that is portable and needs no electrical power. BHAMLA et al. developed a hand-powered centrifuge based on the principle of a whirligig toy [2]. Their centrifuge consists of a paper disc with two holes near the rotation axis. A twisted string is put through the holes and fixed to a handle on each side. With this concept, rotational speeds of up to 125,000 rpm could be achieved. Within 1.5 min, the hematocrit level was attained. The same concept was used by LI et al. in a paper-based centrifuge that contains the essential materials and reagents for enzyme-linked immunosorbent assay (ELISA) [3]. They successfully performed the analysis of carcinoembryonic antigen and alpha-fetoprotein in human blood samples. These current approaches need user interaction for necessary steps in analysis, which is a challenge for untrained users.

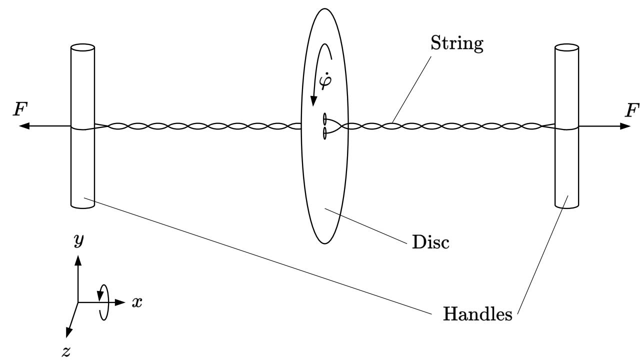

Fig. 1: Schema of the hand powered test platform.

Lab-on-a-disc-systems (LoaD) are centrifugal platforms that automate analysis steps through liquid manipulation. LoaDs are cheap and easy to operate, though need a centrifuge for precise control of angular velocity in test protocols [4]. Because of the cyclical rotation of this system and variation in angular velocity through human input, conventional automation methods of lab-on-a-disc-systems are not used in hand-powered centrifuges.

In this paper, a concept for a hand-powered platform for plasma-based diagnostics is presented and characterised. The system utilizes blood separation and automatic combination of blood plasma with a detection reagent.

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2 System Design

The concept of the hand-powered centrifuge comprises a circular disc, two handles and a twisted string that connects the parts along the axis of rotation (see Figure 1). The spinning cycle consists of an *unwinding* and a *winding* phase. In the unwinding phase, an outward force is applied to the handles. The unwinding of the strings leads to the rotation of the disc. The disc accelerates to maximum angular velocity $\dot{\varphi}_{\max}$, when the strings are parallel. In the winding phase, the applied force falls to zero, and the inertia of the disc rewinds the strings and draws the handles back inwards. The rotation of the disc comes to a momentary halt. The force is reapplied, and the cycle repeats with alternating rotational direction.

During the spinning of the centrifuge, a reagent carrier is routed through the disc along a defined path. The position of the carrier in the disc correlates with the spinning cycles of the centrifuge. Therefore, after a given number of cycles, and thus time of centrifugation, the carrier comes in contact with the plasma without the need of user interaction.

The movement of the carrier occurs at the end of the *winding* phase, respectively the beginning of the *unwinding* phase. Here the angular velocity $\dot{\varphi}$ is zero and the angular acceleration $\ddot{\varphi}$ reaches its maximum. A tangential movement of the carrier relative to the disc takes place. Immediately after that, the disc starts rotating again and the carrier is moving radially outward. The routing is repeated with increasing distance to the rotational axis and alternating rotational direction of the tangential movement. The diameter of the disc is limited, leading to a limited number of routing cycles. To overcome this, a third movement phase is designed where the carrier moves tangentially and inward to the rotational axis at the end of a winding phase. Subsequently, the tangential and radial routing repeats.

To keep the carrier in place during transport and handling of the disc, an angular-velocity dependent mechanism is introduced, which also serves as a velocity control. The spring-loaded latch moves outward at a pre-defined angular velocity (= centrifugal force) with an audible click sound, freeing the carrier initially. It returns to its initial state at low speeds and thus gives the user feedback over reaching a certain rotational speed for each cycle. The functional parts of the disc are shown in Figure 2.

To design the path, the carrier is moving along, the cyclical direction of forces has to be taken into account. In the part of the spinning cycle where the routing occurs, the radial (centrifugal) force is zero and the tangential (inertial) force reaches its maximum. For highest efficiency of the movement and lowest friction, the direction of the movement is equal to the direction of the predominant force. For tangential movement, a cylindrical surface concentric to the disc is used. For the radial movement, the predominant force is the centrifugal force, so a surface in the plane containing the rotational axis is used. The inward movement to the rotational axis follows a logarithmic spiral. There, the angle between the tangential force and the surface is constant. In this case, only the coefficient of friction determines if a movement occurs. Given a sufficiently small coefficient, the routing is ensured along the path of the spiral.

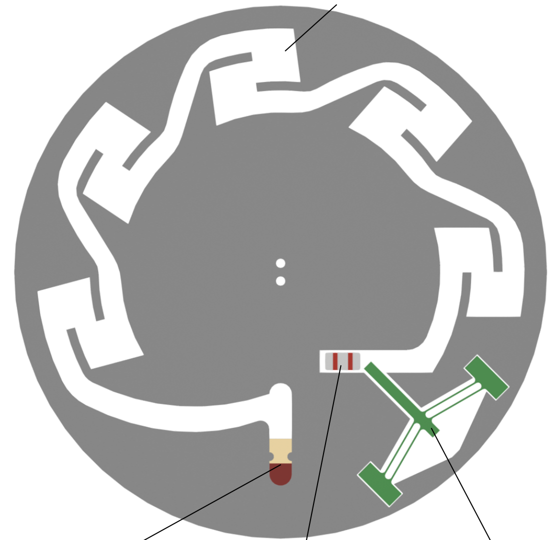

Fig. 2: Structure of the disc's middle layer containing the functional parts.

The geometric parameters of the centrifuge are designed for the highest possible angular velocity of the disc and thus fast extraction of blood plasma. The relation between maximum angular velocity $\dot{\varphi}_{\max}$ and the parameters of the centrifuge is derived from the simplified model of BHAMLA et al. [2]. The distance between the disc and the handle L has to be as large as possible, the width of the disc w_d and the radius of the disc R_d as small as possible.

$$\dot{\varphi}_{\max} \propto \sqrt{\frac{L}{w_\mathrm{d} \cdot R_\mathrm{d}^3}} \tag{1}$$

The disc is manufactured using a Bambu Lab A1 3D-printer (Bambu Lab Ltd., Shenzen, CN) and polylactic acid filament (PLA). The disc has a radius of R_d = 50 mm and a width of w_d = 2 mm. As a reagent carrier, a 3D-printed dummy made of PLA is used. The disc is closed with a 0.5 mm thick transparent polyethylene terephthalate (PET) sheet glued onto with ACRIFIX 1R 0192 (POLYVANTIS GmbH, Weiterstadt, DE). Dyneema D-pro string (LIROS GmbH, Berg, DE) with a diameter of 1 mm and a length of $4L$ = 1 m is used. Aluminium pipes with an outer diameter of 10 mm are used as handles.

3 Material and Methods

3.1 Reagent carrier routing

For evaluation of reagent carrier routing, the movement of the disc with the routing structure and a carrier dummy was recorded with the high-speed camera *Cube6MGE-CM8* (SVS-Vistek GmbH, Gilching, DE) at 1500 fps. The applied force was measured using a *KD40S* force sensor (ME-Meßsysteme GmbH, Hennigsdorf, DE) with a *GSV-2* amplifier (ME-Meßsysteme GmbH, Hennigsdorf, DE). The disc had two holes acting as markers for orientation tracking and calculation of angular velocity. The open-source software *Tracker 6.3.0* was used for automatic tracking of the marker positions [5]. *MATLAB R2024b* (The MathWorks, Inc., Natick, USA) was used for calculating the angular velocity. The movement of the reagent carrier relative to the disc was visually evaluated in the recordings. The force was applied by hand. The experiment was performed five times for each amplitude of the applied force with three different amplitudes of $F_{\max}$ = 30 N, 60 N, 90 N.

3.2 Variation in applied force

The combining of the reagent with the blood plasma occurs after a defined number of spinning cycles of the centrifuge. With increasing applied force, the time of a spinning cycle decreases. At the same time, rotational speed grows, thus the necessary time for centrifugation also decreases. To ensure that sufficient plasma volume is extracted after a given number of cycles, the dependency of routing time and centrifugation time with varying applied force is evaluated.

A 50 mm radius disc was used, with four glass capillary tubes inserted and secured using transparent adhesive film. The tubes contained porcine blood with lithium heparin as an anticoagulant. The blood was sourced from a regional butcher. The disc was recorded with the high-speed camera at 20 fps, and the force was measured with the force sensor. The experiment was performed at three different amplitudes of applied human force ($F_{\max}$ = 30 N, 60 N, 90 N). At the end of every tenth rotation cycle, the fraction of plasma volume was determined on the recording with a measuring tool in the software *Tracker*.

3.3 Calculation of an effective rotational velocity

To compare the blood separation ability of the hand-powered platform to conventional centrifuges, an effective rotational velocity is determined. With this constant effective value, blood is separated in the same time as with the actual rotational velocity of the disc. As a base for calculation, the mathematical model of WONG et al. for blood separation is used [6].

The equations yield the simple relation $\dot{\varphi}_{\text{eff}} = k \cdot \dot{\varphi}_{\max}$ between the effective and the maximum rotational velocity of the disc, with k being a constant factor.

4 Results

4.1 Reagent carrier routing

The measurement shows routing of the reagent carrier at the end of every winding phase (see Figure 3). The tangential, the radial, and the movement on the logarithmic spiral path are successfully performed over the three amplitudes of the applied force. The carrier reaches the end position after the designed number of cycles.

4.2 Variation in applied force

Figure 4 shows the extracted plasma volume as a fraction of the total volume over the number of cycles. The volume of the plasma fraction increases with a higher amplitude of the applied force. The feedback/release mechanism exhibits an audible clicking noise at 4100 rpm on average.

4.3 Calculation of an effective rotational velocity

For determining the effective rotational velocity, the curve of the theoretical model is fitted to the experimental data using a nonlinear least squares optimization (see Figure 5). With that, the k-factor is determined, giving the relation between the maximum and the effective rotational speed ($\dot{\varphi}_{\text{eff}} = k \cdot \dot{\varphi}_{\max}$). The average of this factor is 0.5 over the three amplitudes of the applied force.

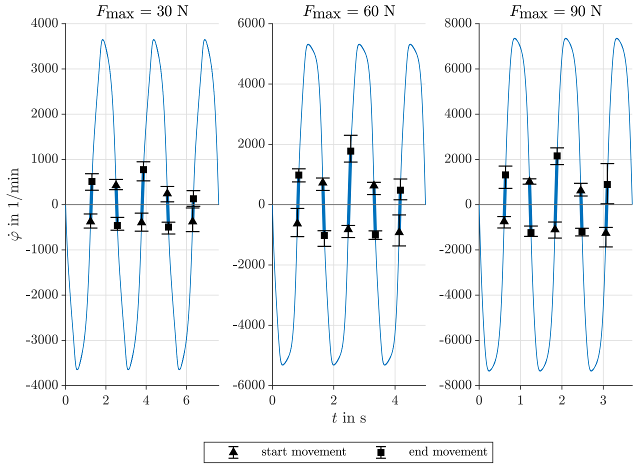

Fig. 3: Rotational velocity of the disc $\dot{\varphi}$ over time t. Thin blue lines show the complete rotation cycle. Thick blue lines show the routing of the reagent carrier.

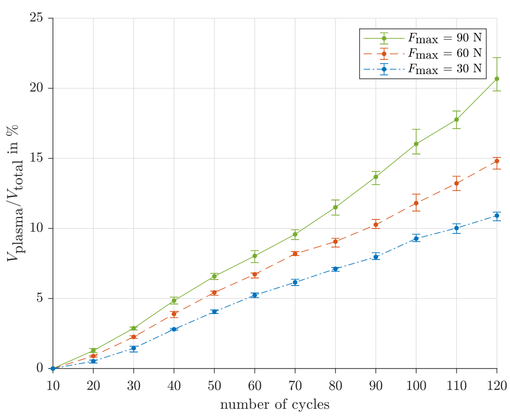

Fig. 4: Plasma volume as fraction of total sample volume with different amplitudes of the applied force.

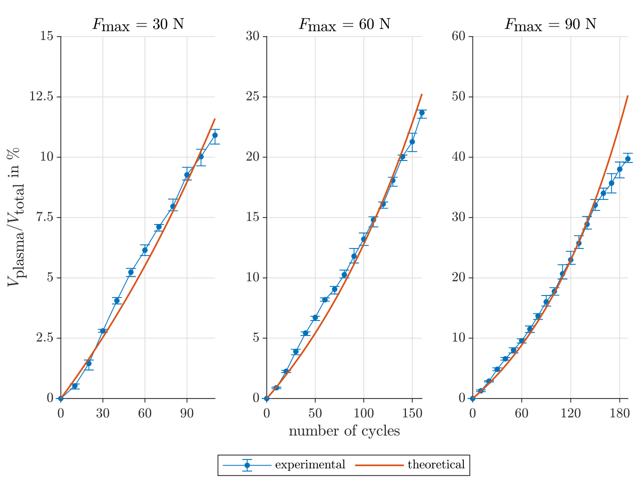

Fig. 5: Plasma volume as fraction of total sample volume compared to the theoretical model.

5 Discussion

The experiments showed the feasibility of the concept of a hand-driven centrifuge for blood separation. Especially, the routing of the reagent carrier was unfailing. However, there are still open challenges which need to be addressed. The maximum number of cycles after the reagent is combined with the blood plasma is limited by the area of the disc. Hence, the amount of blood plasma might be not sufficient for some tests. Consequently, the platform might have to be modified or even upscaled, leading to an increased number of cycles.

In contrast, the disc should be decreased in size, resulting in higher rotational speed. Thus, a faster blood separation and a faster result for the detection of a biomarker can be achieved. Both development goals must be reasonably optimized for future applications.

Yet the concept showed a promising approach for a simple, fast, and cost-effective test platform for plasma-based point-of-care diagnostics.

Author Statement

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