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A diaper pad for diaper-based urine collection and colorimetric screening of urinary biomarkers

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Abstract:

The high prevalence of urinary tract infection in aging adults is a challenging aspect of geriatric care. Incontinence and cognitive/functional impairment makes collection of urine samples difficult and often require either catheterization for sample collection, which is a risk factor for infections, or more lenient criteria for initiating antibiotic treatment.

We report the development of a diaper inlay with absorbent materials, superabsorbent polymer-based valve and chemical reaction pads for rapid screening of urinary tract infection of incontinent diaper-wearing elderly receivers of home care services

The developed diaper inlay was capable of collecting, isolating, analyzing samples and retaining results >8 hours. The diaper inlay can therefore be compatible with the diaper changing routines of nurses in home care services, without requiring much time or effort. A nurse can insert a diaper inlay in a diaper and the results can be recorded during a later diaper change. Although the research focuses on tools for home care services, the nursing home sector has similar problems and may benefit from technological development for rapid screening to avoid unnecessary catheterization and overuse of antibiotics.

Keywords: Biosensors; Capillary flow; Geriatric care; Rapid screening; Urinary tract infection

1.Introduction:

Urinary tract infections (UTIs) are common and occur due to bacteria entering the urethra and infecting a section of the urinary tract. The female bladder is more prone to colonization due to the length of urethra and proximity to vaginal cavity and rectum.¹ UTI is uncommon for males before middle age, where prostatic hypertrophy or prostatitis is more prevalent.² Age, or more appropriately; the degree of independence and functional impairment affect the prevalence and incidence of infection, being the highest for institutionalized or hospitalized elderly.³ For inpatients >70 years old and institutionalized elderly, the prevalence is around 30%.²

According to municipal medical service providers in Sandefjord municipality in Vestfold County, management and treatment of UTI is challenging for patients in nursing homes and receivers of home care services. Many residents in nursing homes are incontinent or have functional impairments and therefore use absorbent products such as adult diapers.^{4,5} The high prevalence of UTI in these populations makes UTI an important condition to monitor. The diagnostic procedure may involve screening with urine

dipsticks and subsequent urine culture depending on the dipstick results.^{6,7} The challenge experienced by home care service providers is the difficulty of collecting urine samples from diaper-wearing incontinent patients. Nurses have time limitations during visits, and residents may not be able to produce a urine sample voluntarily in the available time.

Available options to collect urine samples are: (1) Wait for urination, (2) Catheterization (e.g. indwelling, suprapubic or external) and (3) Collect sample from incontinence product (e.g. diaper). Waiting for a urine sample is inefficient, as it may take several visits to collect a sample, which puts a strain on the human resources as well as introducing unwanted delays in the diagnostic process. Invasive catheterization is efficient, but uncomfortable and increases the risk of infection by introducing a foreign object to the bladder.

A rapid screening solution to the problem was requested from a home care service provider, but is also relevant for nursing homes. Nursing homes does not have the same limitations as home care services, as they may be better equipped with access to e.g. dipstick readers, and they are not subject to the same time restrictions. However, they still have difficulties with collection of urine samples from functionally impaired and incontinent patients, and access to a dipstick reader does not provide a solution to the problem.

Rapid screening cannot reach the level of laboratory analysis and a solution will therefore only attempt to satisfy the purpose of rapid screening as described by Pezzlo, which is to provide accurate information rapidly and to eliminate negative samples.⁶ The metastudy of Devillé et al. found the use of dipsticks useful for ruling out infections in the elderly population.⁸

The main goal is to create a tool for healthcare personnel in home care services and nursing homes to carry out rapid screening of urine from patients who are incapable of providing voluntary urine samples, and to simplify the work routines of the healthcare personnel. Besides the savings in cost and time, such a solution may reduce unnecessary catheterization, over-diagnosed UTI and mis/overuse of antibiotics, thereby improving quality of care.

An estimate based on data from KOSTRA (Municipality-State-Reporting, Norway) revealed that a solution to the described problem could potentially save 100 full time equivalent positions in the municipal nursing and care sector in Norway. A solution to the problem can reduce the work burden of nurses, and thereby reduce burnout. Nurse burnout may lead to reduced quality of care and has also been associated with UTI.^{9,10}

2.Materials and Methods:

Home care service providers are the focus of the problem and a technical solution requires a design compatible with their everyday work routines. Home care service receivers are visited a number of times per day depending on routines and need. For persons wearing adult diapers, there is typically a maximum time between diaper changes. Home care nurses have limited access to equipment, such as dipstick readers, and a solution cannot be perceived as a burden compared to existing methods.

The goals and requirements for a solution are: The solution must not require extensive waiting, invasive procedures, impractical instruments, major changes to the supply chain for consumable products, considerable (re-)education of personnel, or high acquisition cost.

The simplest available source of urine samples under these requirements are from incontinence products. Belmin et al. found good agreement between analysis of urine extracted from diapers worn for 3 hours and urine collected by catheterization, from elderly women with severe incontinence.¹¹ Although agreement in this study was good, it is likely only applicable in ideal cases since urine extracted from a diaper is very likely to be exposed to contamination sources such as fecal matter, skin, anus, or vaginal opening. The degree to which a urine sample is representative of the conditions in the urinary tract may be compromised after a period of exposure to these potential contamination sources. Compared to urine extraction from diaper material, a procedure where fresh voided urine is isolated from the diaper environment, then subsequently analyzed within minutes will retain the representativeness of the sample

A disposable pad with a single-use capillary flow device was designed to be compatible with commercially available adult diapers, and to be placed in a region of likely proximity to urethra. The pad absorbs freshly voided urine and a superabsorbent polymer valve that isolates the urine sample from the diaper environment. The urine is driven by capillary action in porous media to a set of colorimetric reaction pads. After the device is removed from a worn diaper, the resulting colors are visible through a transparent cover layer, and can be compared with a set of reference colors. A disposable pad is preferred over e.g. a customized diaper, which is incompatible with existing supply chains.

This proposed solution appears to satisfy the restrictions posed by the problem and the limitations of rapid screening procedures, without the drawbacks of current methods.

2.1. General device construction

The diaper pad was designed with the intention to be mounted in a diaper with the inlet hole in the support layer (Figure 1 and 2) towards the patient. As urine enters the inlet hole, it comes into contact with the non-woven fabric (NWF) and the cellophane side of a conduction unit (CU), see Figure 2. The sample is transported past the cellophane side of the CU through the protection pad and buffer layer within the SAP frame, to the superabsorbent polymer. The sample is also transported in parallel along the pad conduction strips outside the SAP frame to the reaction pads. Reaction pads in the test layer are separated from the SAP by a partition layer of double sided adhesive tape (DFAT), and the test layer is adhered to the plastic cover with another DFAT partition layer to prevent interference along the plastic cover. As the SAP swells, the cellophane side of the CU expands towards the open inlet hole, and prevents the NWF from coming in contact with liquid from outside the device.

[FIGURE 1]

[FIGURE 2]

2.1.1.Materials

Plastic cover – 1mm PMMA, SAP – Sodium Polyacrylate, SAP frame – 0.3 mm PTFE, DFAT – Double sided medical adhesive tape, Cellophane – 25µm, Test layer – 0.3 mm Polystyrene with Nitrite, Leukocyte Esterase, Blood, Glucose and Protein colorimetric reaction pads, NWF – 20 and 40 g/m², Whatman filter paper grade 41.

2.2.Valve-closing and interference prevention:

Sample capillary flow and reaction chemical diffusion was modelled as electric circuits in the optimization process to ensure that the device operates as intended in relation to the timing constraints for valve-closing, pad saturation and long-term diffusion behavior.

Capillary flow in porous media was modelled as an equivalent electric circuit, see Fig. 3, with capillary pressure as potential and volumetric flow rate as current.¹² A capillary flow resistance can be derived from Darcy's law on the form $R_c = \mu\phi L/kA$, with viscosity μ , porosity ϕ , permeability k , length over which the pressure drop is taking place L . Equations for currents were derived from Kirchhoff's voltage law. The process optimization was performed in iterations by measuring the time necessary to saturate reaction pads and close the valve, and modifying the design based on the equivalent circuit, and repeating until desired behavior was achieved. The optimization parameters were chosen to prevent major changes to the design, while still having a significant impact on the result. Material and dimensions of pad conduction strips were chosen as parameters to optimize pad resistance (R_p), and the amount of SAP was chosen as parameter to optimize the SAP resistance (R_s):

[Figure 3]

$$\begin{bmatrix} R_1 & R_s & 0 \\ R_1 & 0 & R_p \\ 1 & -1 & -1 \end{bmatrix} \begin{bmatrix} I_1 \\ I_s \\ I_p \end{bmatrix} = \begin{bmatrix} V_s + V_1 \\ V_p + V_1 \\ 0 \end{bmatrix}$$

$$\begin{bmatrix} I_1 \\ I_s \\ I_p \end{bmatrix} = \frac{1}{R_1 R_p + R_1 R_s + R_s R_p} \begin{bmatrix} R_p (V_1 + V_s) + R_s (V_1 + V_p) \\ R_p (V_1 + V_s) - R_1 (V_p - V_s) \\ R_s (V_1 + V_p) + R_1 (V_p - V_s) \end{bmatrix}.$$

A similar modeling procedure was used to model chemical diffusion and Interference between reaction pads. Before full saturation of the porous media, the capillary transport will dominate diffusion. As the porous media saturates, transport of reaction chemicals within the device is left to diffusion, which is modelled by electric circuits, through Fick's first law with concentration difference as potential and molar flow rate as current. This gives a diffusion resistance on the form of $R_d = L/DA$. Once the

porous material is saturated, diffusion of chemicals can occur between pads through the saturated porous material that transported the sample to the pads. See Figure 4 for the 6 pads equivalent circuit. The circuit has 2 exterior boundary vertices; a source (a) and a sink (b), and 6 interior vertices (1-6). The interior vertices form a K_6 complete graph where vertex 1 connects to the source and the remaining vertices connects to the sink.

[Figure 4]

The Kirchhoff matrix was constructed as

$$K_{ij} = \begin{cases} \sum_j g_{ij} & \text{for } i = j \\ -g_{ij} & \text{for } (i, j) \in E,^{13} \\ 0 & \text{otherwise} \end{cases}$$

where g is the conductance (weight) of edge (i, j) and E is the set of edges. The matrix K was partitioned according to the sets of boundary and interior vertices and solved for the interior vertex voltages V_i , and the net current I for applied boundary potentials.

$$\underbrace{\begin{bmatrix} A & B \\ B^T & D \end{bmatrix}}_K \begin{bmatrix} V_b \\ V_i \end{bmatrix} = \begin{bmatrix} I \\ 0 \end{bmatrix},$$

$$V_i = -D^{-1}B^TV_b$$

$$I = (A - BD^{-1}B^T)V_b$$

For simplicity an assumption of approximately constant diffusivity and effective cross-section area makes distance the main variable of the interpad resistances. By expressing edge weights as a common pad resistance for each pad, and interpad resistances dependent on distance scaled according to the e.g. smallest distance, the Kirchhoff matrix simplifies so that interior vertex potentials relative to the applied exterior potential difference only depends on the ratio of minimum inter-pad to pad resistance. Effective resistance between source and sink scales with pad resistance, and the ratio of inter-pad to pad resistance determines the difference between currents into the sink-pads relative to source current, See Figure 5. Thus, a high pad resistance ensures low diffusion and uniform sink-current. However, the ratio of pad to SAP capillary flow has the pad resistance in the denominator which makes a high pad resistance inconvenient for optimization of the swelling valve. Hence optimization of the interference prevention must be carried out with this in mind.

[Figure 5]

The process optimization was carried out by measuring the time between pad saturation and the first observable color interference between pads or observable fading of color resulting from diffusion out of pads, then modifying the design parameters, and repeating until desired behavior is achieved. The design parameters to optimize were intertwined with the optimization of capillary flow, through the dimensions and connection of the pad conduction strips compared to the distance of the material connecting the pads.

2.3.Color retention:

Normal dipsticks procedure requires reading within a couple of minutes before the reaction colors are invalid for comparison with references. We investigated how the existing colorimetric reactions behave over time and whether prevention of evaporation, contamination and diffusion can extend the valid reading time in the first turn without major modifications to the recipe. Normal dipstick readings are performed in air, which causes evaporation and oxidation that may affect the colors. By sealing the reactions within a compact package that prevents evaporation and reduces oxidation, the stability of the common biomarker reaction colors may be enhanced to a sufficient degree as to provide a valid reading within an extended period. Reaction colors may have changed and might not be applicable for screening. However, if the reaction colors are still distinguishable for different concentrations, they may still be useful for classification according to a new set of references.

Reaction colors from optimized prototype devices saturated with artificial urine for specific concentrations of biomarkers were recorded with a scanner frequently at the start, and less frequently over time, for approximately 20 hours. Color data was extracted as average pixel values from 15 devices in parallel for each time step, repeated for each concentration level.

2.4 Analysis

Analyses were performed in R ('exactRankTests' and 'PropCIs' packages) and Matlab (Prtools package).^{14,15,18}

One-sample Kolmogorov-Smirnov (KS) test was used to test normality of saturation time and valve closing time, and a two-sample KS test to test whether saturation time and valve closing time was from the same distribution. A paired Wilcoxon signed rank test was used to test for zero median between time datasets, and to establish Wilcoxon signed rank confidence intervals (WCI). The rate of successful saturation and valve closing was given with a Clopper-Pearson exact confidence interval (CPCI).¹⁶ Significance level set at 0.05.

Nonlinear Fisher mapping was used to reduce the dimensions of color data from 3 (R,G,B) to 2 (Feature 1, Feature 2).¹⁷ The resubstitution error for a quadratic classifier as a function of time was used to define the validity period by minimizing resubstitution error in datasets for truncated time series, where reaction colors for different biomarker levels could be distinguished.

3.Results:

3.1.Valve-closing and saturation:

After iterative pad and SAP resistance optimization, the optimized device was fabricated, assembled and tested. A median of 12 urine drops (100 μ L/drop) were

dispensed in the inlet of 27 packaged devices, and the recorded time necessary to observe saturation and valve-closing was a pseudo-median (Hodges-Lehmann estimator) of 7.025 (95% WCI 6.8-7.3) and 7.375 (95% WCI 6.95-7.65) minutes respectively (see Boxplot in Fig. 6). Normality of recorded time was rejected with KS test ($p < 0.0001$), therefore nonparametric methods were used. A two-sample KS test could not reject that valve-closing and saturation time were from the same continuous distribution ($p = 0.076$). A paired Wilcoxon signed rank test for zero median between the two data sets was not rejected ($p = 0.062$).

[Figure 6]

Out of 27 devices, each with 6 reaction pads, 4 devices experienced a failure where one reaction pad was not saturated, which gave a sample proportion $\hat{p} = 0.852$ (95% CPCI 0.663-0.958). The source of the failure was identified as misalignment, which essentially set the affected pad resistance to infinity. Improvements to fabrication and assembling processes reduced the failures to zero in a batch of 212 tests $\hat{p} = 1$ (95% CPCI 0.982-1), hence the improved prototype batch did not have a sufficient sample size to experience a failure.

3.2. Interference and Color retention:

For 27 tests with optimized design for interference prevention there were no observable interference within the desired time interval (8 hours) or after the extended duration (22 hours). In Figure 7 the bottom left reaction pad (protein) shows sign of a green color in the lower right corner. but from the Protein reaction itself. The uneven colors became uniform after approximately 30 minutes.

[Figure 7]

The nonlinear fisher mapped datasets, see Figure 8, exhibit a low amount of overlapping samples for all timesteps except for the Glucose and Leukocyte esterase marker. By separating the data into an initial set and a final set based on minimization of resubstitution error, the collected Glucose and Leukocyte Esterase data could be classified reasonably well.

[Figure 8]

4. Discussion

A disposable absorbent pad was developed for urine collection and screening in diapers. After the pad absorbed a small volume of urine, the chemical reaction pads

saturated and the SAP valve sealed the inlet in approximately 7 minutes. There were no observable chemical interferences^s between the pads in the recorded or desired time interval. The reaction colors were sufficiently stable to distinguish three concentration levels for each biomarker within the desired time interval defined from 30 minutes to 8 hours. The device therefore satisfies the requirement initially set for the application. Saturation and valve-closing time were consistent, the reaction colors were distinguishable, interference and external contamination was preventable. With these features, the device can collect and screen urine within a home care service environment without requiring much effort or time from a nurse. The diaper pad can be inserted by one nurse and removed and analyzed by another nurse at a later point in time. A smart phone app is also under development to simplify and provide a more objective read-out, than can be achieved by the 'naked eye'.

Time is a challenging factor of this problem. It is possible to record the time for device insertion/removal in a diaper, but this will likely not correspond to the reaction time, as the time between patient urination and device removal cannot be assumed known based on diaper change routines. Asking patients to record the time when they urinate is not a viable solution due to incontinence and the varying degree of cognitive ability of the relevant patient group. The target read-out time based on the experiments is between 30 minutes and 8 hours. The upper bound can be estimated based on the diaper change routine, but the lower bound is uncertain. However, the moisture indicator (the upper left pads of the devices in Figure 7) mounted onto an empty reaction pad changes color on initial saturation, but does not color the underlying pad until approximately 30 minutes after saturation. Therefore the moisture indicator pad can both act as an indication of saturation as well as an indication of time.

The Leukocyte Esterase reaction and Glucose reaction are enzymatic, but were sufficiently stable when tested with artificial urine, albeit less stable than desired. To expect similar or improved results in clinical test with human samples, the use of inhibitor will likely improve the stability over time.

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Conflict of interest

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Figures and figure captions

Fig. 1 Device layers

Fig. 2 Cross-section view of packaged device, dimensions not to scale

Fig. 3 Equivalent capillary flow circuit, where subscript 'p' – pad, 's' – SAP, and '1' is the remaining porous materials from inlet to 'p' and 's'

Fig. 4 a) Layout of pads, b) Equivalent circuit for diffusion between a chemical concentration source (a) connected to (1) and a sink (b) connected to the remaining pads (2-6)

Fig. 5 The ratio of currents in sink-connected pads to source-connected pad. a) Source connected to pad 1. Equivalent to 2,5,6 due to symmetry. b) Source connected to pad 3 (Elements in K changes accordingly). Equivalent to 4 due to symmetry

Fig. 6 valve-closing time: pseudo-median = 7.025, (95% WCI of 6.8 - 7.3) minutes. Saturation time: pseudo median 7.375, (95% WCI 6.95 - 7.65) minutes. Paired Wilcoxon signed rank test Pseudo-median -0.2 (95% WCI -0.35 - 0).

Fig. 7 A set of representative interference tests

Fig. 8 Nonlinear fisher mapped plots of relevant biomarker reactions in sealed environment. Quadratic classifier rules for all plots except for h) which is mixed gaussian. a) Nitrite 0-22.5 hours, 0% resubstitution error, b) Proteins 0-22.5 hours, 0% error, c) blood 0-8 hours, 0.12% error, d) Glucose 0-19.5 hours, 31% error, e) Glucose initial color, 4.4% error, f) Glucose 30 min-19.5 hours, 8% error, g) Leukocytes 0-19.5 hours, 20% error, h) Leukocytes 0-30 min, 11% error, i) Leukocytes 30min-19.5 hours, 3.3% error.