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Designing lab-on-a-chip systems with attribute dependency graphs

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Abstract

Lab-on-a-Chip (LOC) products for point-of-care diagnostics have gained significant attention. However, there is a lack of systematic approaches for LOC product development. To address this, we introduce an Attribute Dependency Graph exemplary for a magnetophoretic LOC system for pathogen detection. This model organizes dependencies between the design variables and crucial quantities of interest, such as detectability, cost per test, and test duration. The obtained model helps to manage design complexity and can be adapted to other LOC approaches.

Keywords: dependency modelling, methodical design, product development, complex systems, lab-on-a-chip

1. Introduction

In recent decades, substantial advancements within the microchip industry have given rise to point-of-care diagnostic tools known as lab-on-a-chip (LOC) systems (Reyes *et al.*, 2021). LOC systems represent a miniaturization of complex laboratory procedures thus enabling rapid on-site testing (Ducrée, 2019). The advantages lie in the small required volume of the sample and the rapid processing times (Chin *et al.*, 2012). LOC products find applications in biological and biomedical domains, encompassing fundamental biology research, clinical use, food safety, and environmental monitoring (Lim *et al.*, 2010). Common functionalities include particle or cell mixing, separation, and trapping (Munaz *et al.*, 2018).

A prevalent approach involves employing continuous microfluidic or millifluidic flows for separating target particles from the fluid (Bruus, 2008). Employing continuous flow offers various benefits, such as integration for process automation. However, it poses a conflict between achieving high throughput and maintaining high resolution (Pamme, 2007). The increasing demand for microfluidic and millifluidic LOC products underscores their promising market prospects (Reyes *et al.*, 2021).

Existing literature extensively covers academic proof of concept (Chin *et al.*, 2012) and the diverse components of LOC products (Lim *et al.*, 2010). However, from a product development standpoint, there's a lack of overarching principles to manage the complexity arising from the system's diverse requirements and design solutions. Most LOC systems are tailored for custom applications, neglecting synergy effects regarding standardized components and methodologic design. Heintz et al. (2016) advocate for a unified millifluidic platform approach to streamline the product development process. Ducrée (2019) introduces a qualitative framework that maps input parameters to Key Performance

Indicators (KPIs) of LOC systems through qualitative linkages. This mapping aims to ensure performance while considering manufacturability and scalability.

1.1. Paper objectives

Rötzer et al. (2022) introduce a method for characterizing the causal link between design variables (directly controllable) and quantities of interest (not directly controllable) called the attribute dependency graph. Its primary advantage lies in eliminating circular dependencies and enhancing transparency in complex system designs. The attribute connections are established based on equations and known relations. This method is beneficial for LOC system development due to the existence of multiple physical models describing micro- and millifluidic system behaviours for various separation strategies.

This study constructs an attribute dependency graph for a magnetophoretic millifluidic separation system designed for bacteria detection. It concentrates on crucial quantities of interest (QoIs) such as detectability, test costs, and duration. Detectability ensures the system's reliability in identifying the target particles in the fluid. Considering and optimizing costs and time are crucial to sustain the system's competitiveness against other point-of-care diagnostics and LOC products. The relationships between design variables (DVs) and QoIs are derived from physical models for millifluidic separation problems. The resulting model is adaptable for different separation strategies and various QoIs. This versatility is demonstrated by adapting the system into a magnetophoretic separation device aimed at maximizing particle separation efficiency.

2. State of the art

2.1. Lab-on-a-chip and magnetophoresis

LOC systems currently attract significant attention in both research and product development due to their applicability as point-of-care diagnostic devices, necessitating small sample volumes and rapid processing times. Microfluidics companies present diverse design options encompassing material, manufacturing, sample handling, treatment, fluid control, actuation, mixing, and signal detection. One of the first successful LOC implementation is Abbott's® 1983 launched iSTAT device, capable of detecting various blood chemistries, coagulation factors, and cardiac markers (Chin *et al.*, 2012).

The technology utilized in LOC systems varies significantly based on the intended application. Commonly, these systems are employed for particle separation, trapping, or sorting, categorized into passive and active techniques. Passive techniques like filtration function without external fields, while active techniques, including dielectrophoresis, optical and acoustic methods, and magnetophoresis, rely on external fields to manipulate particle trajectories (Sajeesh and Sen, 2014).

Magnetophoresis stands out among separation techniques due to its notably high selectivity and specificity. This technique primarily focuses on attracting magnetic particles. However, non-magnetic target particles necessitate magnetization, often achieved by attaching functionalized magnetic nanoparticles, to enable their attraction. These magnetic nanoparticles exhibit superparamagnetic behaviour, weakly aligning with the magnetic field. Iron oxide nanoparticles serve as typical examples of superparamagnetic materials (Munaz *et al.*, 2018).

In academic settings, magnetic LOC systems have demonstrated efficacy in various applications, such as *E. coli* bacteria separation, malaria-infected red blood cell detection, yeast cell separation, and algae separation (Reiter *et al.*, 2022). Commercial success of millifluidic magnetophoretic LOC systems has still been limited. While there are various companies offering milli- and microfluidic solutions (µFluidics®, Creative Biolabs®), we were not able to identify any magnetophoresis-based LOC products available on the market today. Announcements from Philips® and bioMérieux® regarding a handheld product for rapid protein analyte detection were made (Chin *et al.*, 2012). However, this product never reached commercialization.

2.2. Product development for lab-on-a-chip systems

The components of a LOC system vary based on specific use cases. Examples of components employed in microfluidic and millifluidic applications include (Lim *et al.*, 2010):

- Valves and pumps

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- Fluid guiding unit, transporter, separator
- Detector: sensors and chips
- Electronic controller, power supply, and data handling systems

In addition to instrumentation, considerations in developing a LOC system encompass materials, manufacturing methods based on dimensions, features, and surface properties, as well as the sample itself and, if relevant, reagents - such as liquid properties, reagent quality, and loaded volumes. Furthermore, external factors like ambient conditions (e.g., pressure) contribute to the system's functionality (Ducrée, 2019).

Ducrée (2019) categorizes these elements and characteristics as input parameters. As depicted in Figure 1, these input parameters are linked to Key Performance Indicators (KPIs), which serve as metrics to assess the performance of the intended application. These connections can be direct or indirect. However, the specific connections between inputs and KPIs, the available inputs, and the impact of each input on a KPI are not explicitly specified.

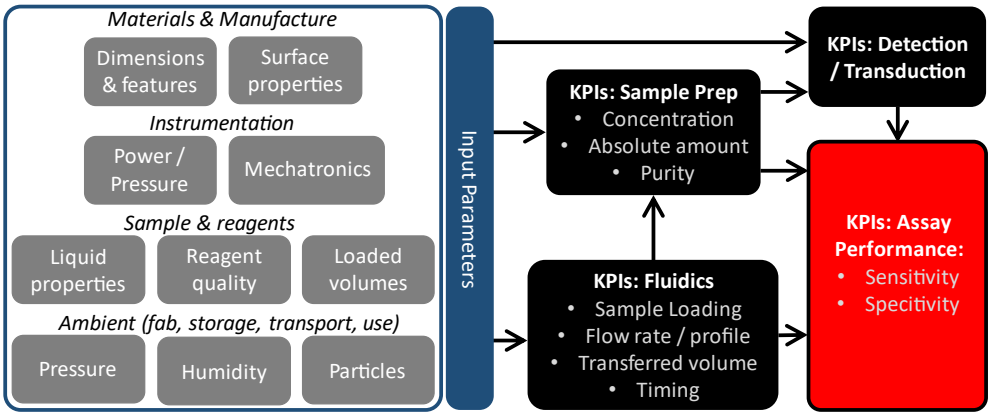

Figure 1. Input parameters of the LOC system are mapped onto the KPIs (Ducrée, 2019)

The term "method" is often understood in the literature as a rule-based and planned sequence of activities (Lindemann, 2009). Numerous methods are available to model attribute dependencies of a product and the corresponding development processes. An overview of product dependency models can be found in Rötzer et al. (2022). Examples are axiomic design, the function-behaviour-structure framework, extended design structure matrices, effect graphs, direct acyclic graphs, and attribute dependency graphs. To the author's knowledge, there are currently no quantitative dependency models specifically applied to LOC systems in the literature.

2.3. Attribute dependency graphs

> *"Visualisation is one of the most effective means to support communication since humans perceive about 70% of all information visually." (Eiselt et al., 2013)*

Rötzer et al. (2022) address this statement by constructing cause-and-effect models for design decisions avoiding circular dependencies, the so-called ***attribute dependency graph*** (ADG). ADGs adhere to the graph elements outlined by Diestel (2017). Essentially, ADGs take the form of polyhierarchical directed graphs with unweighted edges. They prohibit connections between nodes at the same hierarchical level and disallow loops. Nodes within this graphs symbolize the objectively measurable attributes of the system. ADGs consist of the following elements:

- ***Design variables***: DVs are directly controllable attributes, such as the geometry of a millifluidic channel. DVs are positioned at the base of the graph. Some DVs may align with the input parameters delineated in Ducrée (2019).
- ***Design parameters***: Not all input parameters can be influenced. For instance, the cell size of target particles remains fixed. These unalterable attributes are termed design parameters. Design parameters are generally excluded from ADGs as they do not significantly impact the design process. However, their values are considered in equations and simulation models.

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- ***Quantity of interest***: QoIs are attributes that are not directly controllable and reside at the top of the ADG. QoIs represent attributes used to evaluate the system's performance. For instance, QoIs can be comparable to the KPIs in Ducrée (2019).
- ***Intermediate attributes***: Positioned between DVs and QoIs, intermediate attributes prevent the ADG from becoming a black box, thereby enhancing transparency regarding dependencies. The determination of the necessary quantity of intermediate attributes lies within the designer's discretion, seeking to achieve an equilibrium between comprehending the system and averting undue complexity in the model.

In general, ADGs are time-independent, and follow a bottom-up approach, culminating in the mapping toward the QoIs. While requirements can be acknowledged through statements alongside QoI attributes, they aren't encompassed as distinct attributes themselves. The connections within ADGs are established via functions, characteristics, distributed quantities, and simulation models. An outline of these principles is depicted in Figure 2. In the subsequent use case, ADGs are used to manage the design complexity of LOC systems.

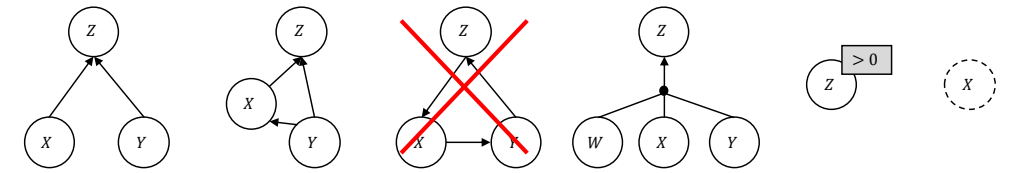

Figure 2. Rules for the ADG design (Rötzer *et al.*, 2022)

3. Development of an attribute dependency graph for a magnetophoretic lab-on-a-chip system

3.1. Scenario description

In our scenario, the objective is to detect target particles, e.g., bacteria, present in tap water using an impedance measurement chip. Initially, ***magnetic nanoparticles*** (MNPs) are modified with bacteria-specific antibodies. These antibodies have a high affinity for the target particle. The combination of MNPs bound to a target particle is referred to as a ***magnetized target particle*** (MTP) in the subsequent stages. A magnet affixed to the sensor serves to separate the MTP via magnetic forces, guiding them onto the sensor. Other particles or objects within the flow remain unaffected by the magnet and continue along their trajectory. The system shall be able to test large sample volumes within a short time, therefore classified as a millifluidic system. The configuration of the channel is illustrated in Figure 3. Subsequently, the relationships among various design variables and quantities of interest are deduced based on this setup.

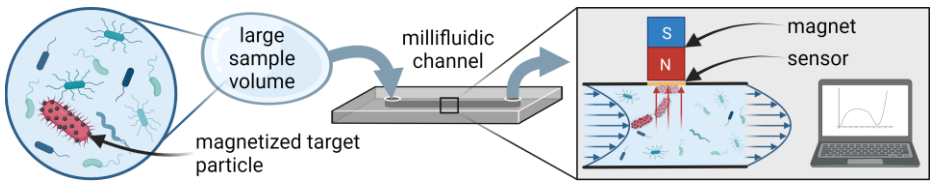

Figure 3. Schematic visualization of the magnetophoretic LOC system (Created with BioRender.com)

3.1.1. QoI 1: detectability

Detectability ensures that the sensor can detect the target particles. The ***limit of detection*** is defined as the lowest concentration of the target particle in a sample that can be consistently detected (Armbruster and Pry, 2008). For instance, the sensor shall detect a concentration $C_{p,req}$ of one bacterium within 100 ml of fluid. Subsequently, the limit of detection of the system must be equal or lower than $C_{p,req}$.

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To generate an impedance signal ensuring positive detection, the sensor requires a specific number of target particles on its surface $n_{p,req}$. This delineates the threshold quantity of target particles necessary to trigger a sufficient sensor signal. The ***threshold*** $n_{p,req}$ isn't fixed but depends on the ***noise*** caused by ambient conditions, for instance, by the presence of non-target objects such as other bacteria or unbound MNPs. In our context, the threshold is mainly influenced by the MNPs within the fluid. An optimal concentration of MNPs C_{MNP} binding to the target particle must be identified. If this concentration is excessively high, the number of MNP reaching the sensor $n_{MNP,S}$ increases, which elevates noise and thus the threshold, impairing the system to detect the target particle. Therefore, finding the optimal C_{MNP} that binds enough particles without significantly elevating the threshold is crucial. Characteristic curves depicting the relationship between C_{MNP} and the fraction of target particles that get magnetized need to be established or determined. The relation of threshold and noise needs to be specified through laboratory and calibration tests. For the ADG the relation $n_{p,req} = f(n_{MNP,S})$ is used, where the function $f(n_{NMP,S})$ represents a sensor and ambient condition specific characteristic.
The quantity of MTP reaching the sensor can be calculated using the minimum allowable concentration of target particles in the fluid $C_{p,req}$, the fluid volume of the test V_{test}, and the fraction of captured particles p_p. The latter denotes the percentage of MTP in the flow that ultimately arrive on the sensor's surface. Equation 1 enables the determination of the number of MTP reaching the sensor surface $n_{p,S}$ from these three values. The number of unbound MNP reaching the sensor $n_{MNP,S}$ can be obtained similarly with the assumption that the bacterium's influence on the MTP trajectory is negligibly small. This assumption is valid if the volume of the target particle is significant smaller than the MNP agglomerate's volume. If this is the case, $n_{MNP,S}$ can be calculated with equation 2.

$$n_{p,S} = C_{p,req} V_{test} p_p \tag{1}$$

$$n_{MNP,S} = C_{MNP} V_{test} p_p \tag{2}$$

Consequently, we obtain our first quantity of interest, the detectability, outlined in equation 3. The ADG derived from these relationships is depicted in Figure 4. The attribute $C_{p,req}$ is a requirement-derived value and remains unalterable. Hence, $C_{p,req}$ is classified as a design parameter and does not appear in the ADG. As p_p cannot be directly influenced, it doesn't qualify as a design variable but serves as an intermediate attribute. Therefore, it is required to extend the ADG deriving the design variables related to the attribute p_p.

$$D = n_{p,S} - n_{p,req} \tag{3}$$

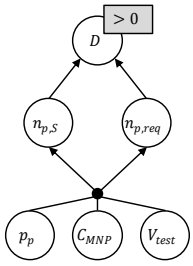

Figure 4. Partial representation of the ADG for the first QoI: detectability

In practice, the fraction of captured particles p_p is obtained using an in-house simulation model based on analytical equations. More information about the model will be provided in forthcoming publications. This model relies on deriving the trajectory of a MTP by calculating the induced velocity resulting from the dominant acting forces, primarily the magnetic forces F_{mag} and the drag forces F_D, as emphasized by Chong et al. (2021). Pavlovic et al. (2022) suggest considering particle interaction due to magnetization, while asserting that gravity force F_g and buoyancy F_l can be disregarded. Nonetheless, the decision of which forces must be considered is influenced by the system's scale and magnetic field strength. With increasing distances, magnetic forces notably diminish. Moreover, at lower concentrations of C_{MNP}, the particles' interaction may be negligible.

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Both concentration and magnetic field notably affect the volume of the MNP V_{MNP}, as they contribute to increased particle agglomeration. Therefore V_{MNP} represents a distributed quantity. In our model, equation 4 is obtained for the force equilibrium for an MTP. In alternative scenarios and scales, different forces such as dielectrophoretic forces, acoustic forces, or elastic forces may be relevant (as indicated by Cha et al. (2022)).

$$\sum F = F_{mag} + F_D + F_g + F_l \tag{4}$$

According to the second law of Newton, this implies an acceleration of our particle. However, considering the low Reynold numbers, this inertia force can be neglected, so that $\sum F = 0$ (Chong *et al.*, 2021). The combination of gravity force F_g and buoyancy F_l results in equation 5, wherein g represents the gravity force, V_p the volume of a particle and ρ_p and ρ_f the density of the particle and fluid, respectively (Lim *et al.*, 2010).

$$F_g + F_l = gV_P(\rho_P - \rho_f) \tag{5}$$

The magnitude of the magnetic force is contingent on the magnetic field gradient, which, in turn, relies on factors such as magnet material, dimensions, and the position of the particles within the magnetic field. An approximation of a magnetic field strength H can be obtained, for instance, computationally using software like COMSOL Multiphysics® (Chong *et al.*, 2021). The magnetic field strength depends on the length L_{mag}, diameter d_{mag}, and class G_{mag} of the magnet. The resulting forces of the magnet on the particle can be calculated utilizing equation 6. $M_{p,m}$ denotes for the mass magnetization of the MNP, and μ_0 represents the permeability of free space.

$$F_{mag} = V_p \rho_p M_{p,m} \mu_0 \nabla H \tag{6}$$

The MTP, which are agglomerates of MNP together with the target particles, are modelled as spheres moving through the fluid. This movement is characterized by the stokes drag F_D in equation 7, where η denotes the kinematic viscosity, r_p stands for the particles' radius (that are assumed to be spheres), v_p represents the particle velocity, and v_f the velocity of the fluid (Chong *et al.*, 2021).

$$F_D = -6\pi\eta r_P(v_p - v_f) \tag{7}$$

The movement of the MTP relative to the fluid $v_{p,rel} = v_p - v_f$ can be calculated using equation 4-7 via equation 8.

$$v_{p,rel} = \frac{\rho_p V_p}{6\pi\eta r_p}\left[M_{p,m}\mu_0 \nabla H + g\left(1 - \frac{\rho_f}{\rho_p}\right)\right] \tag{8}$$

However, this velocity is not included in the ADG due to its time-dependent nature. It's possible to calculate the duration required for the particle to be attracted t_{attr}. To determine the current position of the particle accurately, consideration must be given to the fluid flow within the channel that transports the particles.

Several models exist to analytically compute the flow of fluid through channels of specific shape, often referred to as Poiseuille-flow (Bruus, 2008). For simplicity, the channel can be modelled as a 2D-channel, comparable to an infinite parallel channel. The velocity can be calculated using equation 9, where h represents the height of the channel and z denotes the current position within the channel. Δp corresponds to the pressure difference over the channel of length L. For laminar flow, the velocity has just a component in main flow direction (x-direction).

$$v_f(z) = \frac{\Delta p}{2\eta L}(h - z)z \tag{9}$$

A duration, known as t_{pass}, can be computed to signify the time taken for a particle to traverse through the channel. If $t_{attr} < t_{pass}$, the particle becomes attracted. The volume flux $\dot{V}$ can be directly regulated, for instance, through a syringe pump. The pressure difference Δp is obtained by equation 10, using $\dot{V}$, h, η, and the channel width b.

$$\Delta p = \frac{12\eta L}{h^3 b}\dot{V} \tag{10}$$

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Combining both velocities allows for the calculation of the MTP's trajectory and determines whether the MTP misses or lands on the sensor. Considering the velocity profile, the fraction of captured particles from the total flow p_p can be calculated, consequently establishing the number of MTPs reaching the sensor during a single test (equation 1). An in-house simulation model is employed to compute these trajectories. This model utilizes the design variables to determine the fraction of captured particles p_p.

From the shown equations, characteristics, and models, the first part of the ADG is obtained, outlining the causal connection from the derived design variables to the quantity of interest detectability. One could opt to reduce the model's complexity by fixing the values of some DVs. However, it is recommended to avoid this approach as it hinders an assumption-free design (Rötzer *et al.*, 2022). In this specific scenario, the magnet dimensions can be chosen, and the sensor dimensions d_{sensor} may be variable by choosing a different sensor's size. The channel is characterized by the DVs b and h. The variables $\dot{V}$, V_{test} and C_{MNP} can be influenced directly and are thus DVs. The resulting ADG is shown in Figure 5.

While requirements cannot be directly incorporated into the ADG, they can be visualized by associating them with an attribute. For instance, the requirement for detectability D is that its value should be above zero, ensuring the sensor's capability to detect the presence of target particles in the sample. In this case the limit of detection is lower than $C_{p,req}$ and the requirement is fulfilled.

The design parameters are considered in the models but are not explicitly depicted in the ADG. For instance, $C_{p,req}$ is a crucial parameter. These values remain fixed throughout the design process and are therefore not of interest for the designer.

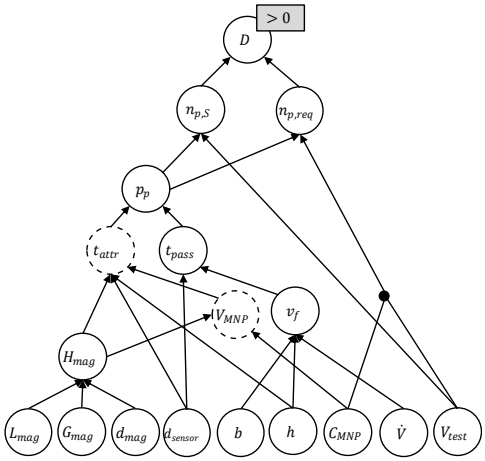

Figure 5. The complete ADG of the first QoI: detectability

3.1.2. QoI 2: costs

The total costs K_{tot} can be segmented into two categories: recurring costs incurred per test K_{test} and the one-time expenses associated with reusable equipment K_{equip}. Recurring costs are influenced by whether the fluidic unit and sensor can be reused. Lab-on-a-Chip (LOC) systems are often designed for single-use purposes (Ducrée, 2019).

The expenses per test encompass material and manufacturing costs attributed to the millifluidic channel K_{CH}, contingent upon factors like channel geometry, material choice, and manufacturing method. In our model, material and manufacturing are designated as design parameters and are thus not explicitly represented within the ADG. However, from a Design-for-Manufacture perspective as in Ducrée (2019), one could also consider these attributes as DVs, such as material costs.

Recurring costs further encompass the expenses related to the costs of sensor K_{sensor} and functionalised MNP K_{MNP}. The choice of the pump is influenced by the pressure and volume flow of the system, impacting the pump's characteristics and thus its cost K_{pump}. Additionally, the cost of the magnet K_{mag} is influenced by the magnet's design variables. Other components or costs not addressed within the ADG are either independent of our chosen design variables and designated as fixed design parameters.

A quantitative connection between DVs and costs might not always be feasible, as they are subjected to non-quantifiable influences, such as negotiation.

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3.1.3. QoI 3: duration

The duration of a single analysis constitutes the final QoI within the ADG. Apart from other time demanding steps that operate independently of our ADG, the duration t_{test} primarily depends on the time required for the fluid volume to traverse our channel, as outlined by equation 11. Depending on the selected preprocessing steps, other durations may also emerge within the ADG.

$$t_{test} = \frac{V_{test}}{\dot{V}} \tag{11}$$

3.1.4. Further QoIs and DVs

Additional QoIs could be integrated, such as sustainability considerations involving the channel's material and manufacturing processes, leading to the derivation of a CO2-Equivalent value. Also, manufacturability is an indicator that needs to be considered in the design process. Nevertheless, the three initially considered QoIs have been identified as the primary determinants of the product's competitiveness. If additional QoIs are introduced, it's crucial that they are quantifiable and can contribute substantially to the overall assessment.

The number of DVs depends on the design's flexibility, influenced by factors such as the manufacturing process, and on the simplification of the system. Generally, there is no strict limit to the number of DVs. For better handling, the design process can focus on the DVs with substantial impact on system performance, such as volume flux, channel dimensions, and MNP concentration (Chong et al., 2021).

4. Results and discussion

4.1. Attribute dependency graph of the lab-on-a-chip system

The resulting bottom-up mapping visualized by the ADG is depicted in Figure 6, revealing ten DV at the bottom. These attributes can be influenced within the design process. The dotted circuits signify distributed quantities, such as the variability in MNP-agglomerate volume V_{mnp}, leading to a distributed attraction time. However, the fraction of captured particles p_p is derived from V_{mnp}, ultimately yielding a single value.

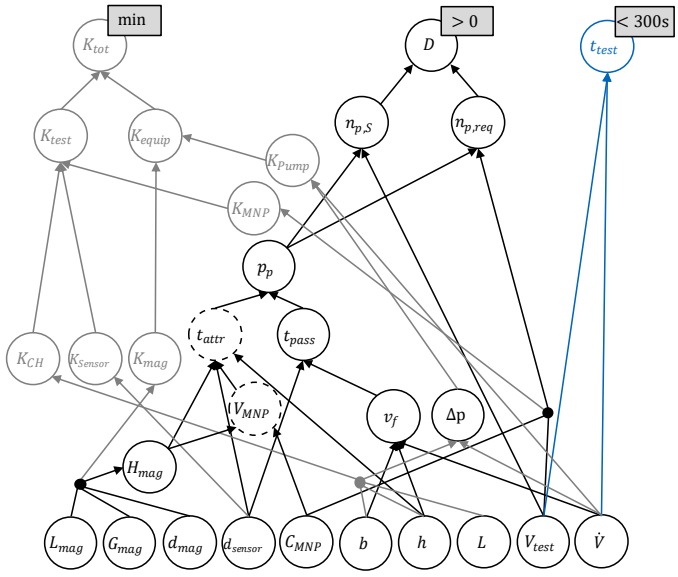

Figure 6. Complete ADG of the magnetophoretic LOC system for the determined QoIs

The relationship between t_{attr} and t_{pass} is insightful in revealing the DVs that affect the particle's duration within the channel. The magnet notably impacts t_{attr}, whereas $\dot{V}$ and the channel geometry significantly dictate the time of the particle to traverse the channel. Interestingly, the overall test duration t_{test} appears largely independent of the entire system. The cost is influenced by each DV. Recurring costs stem from sensor costs, channel geometry, and MNP costs.

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4.2. Adaptation examples for other lab-on-a-chip strategies

An alternative approach could involve utilizing the LOC device to maximize the extraction of MNP. This would change the detectability towards the fraction of captured particles p_p. It appears that the system's fundamental architecture remains relatively unchanged. However, altering the QoIs impacts the optimal values for the DVs. In this scenario, the number of intermediate attributes reduces. The resultant ADG reflecting these modifications is illustrated in Figure 7.

Another potential modification could involve adopting the separation strategy, for instance, to an electrophoretic separation. This adjustment would significantly change the DVs, as the magnetic field would be replaced by an electric field. Consequently, the forces affecting a moving fluid would change, subsequently impacting parameters like t_{attr} and the particle trajectory. Additionally, there might be a change in the type of functionalised MNP. However, despite these alterations, the QoIs would remain unchanged.

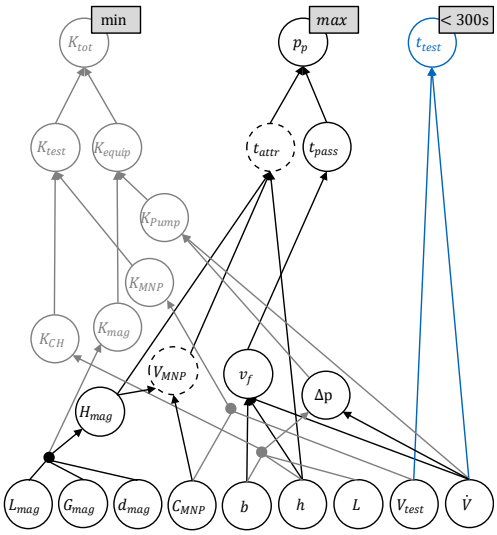

Figure 7. Adapted AGD due to the changed QoI detectability to p_p

5. Conclusion and outlook

An attribute dependency graph has been developed for a magnetophoretic millifluidic lab-on-a-chip system for bacteria detection in tap water. The ADG has been derived from established relations in micro- and millifluidics, along with magnetophoresis. The main quantities of interest detectability, costs, and test duration have been connected and ten design variables are identified. Analysis of the ADG reveals that all DVs impact detectability, while most influence system and test costs. However, test duration is notably dependent on only a few DVs.

This model addresses the preliminary design stages of LOC products from a systems engineering perspective. It introduces a quantitative methodology for developing complex LOC systems. The ADG helps the designer to manage design complexity. Attributes at the bottom of the graph can be influenced directly by the designer. Notably, changing the volume flux has a significant influence on the entire system. Based on the ADG, the next step would be to optimize the system based on the QoIs. The shown requirements are either constraints in the optimization process (equality and inequality constraints) or objective functions (QoIs that shall be minimized or maximized). The quantitative connections within the ADG enable direct application of Solution Space Engineering (Zimmermann and Hoessle, 2013).

ADGs can help to leverage existing synergies in LOC system's development, making the development more responsive and flexible to market demands. For instance, the target particle hasn't been specified in the derived ADG. Further optimization procedures may reveal optimal design variables specific to different target particles. Additive Manufacturing could subsequently enable target-specific rapid manufacturing of LOC systems.

The ADG allows for quick changes of the dependency structure. There are numerous alternatives for both QoIs and DVs, no singular solution exists, as the ideal approach varies based on the designer's

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objectives. The designer can zoom in and out without losing information by adding or excluding hierarchical levels. In next steps, aspects like manufacturability or scalability can be included as QoIs in the ADG, because of their importance on the product's success (Ducrée, 2019).
Various LOC strategies lead to different pre- and post-processing steps, making standardization challenging. Further investigations into applying this method to different strategies and objectives are necessary to fully assess its strengths and limitations in the context of LOC product development.

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