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Design and simulation of biomimetic microfluidic designs to achieve uniform flow and DNA capture for high-throughput multiplexing†

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High-throughput multi-analyte point-of-care detection is often constrained by the limited number of analytes that can be effectively monitored. This study introduces bio-inspired microfluidic designs optimized for multi-analyte detection using 38–42 biosensors. Drawing inspiration from the human spinal cord and leaf vein networks, these perfusion-oriented designs ensure uniform flow velocity and consistent molecular capture while maintaining spatial separation to prevent cross-talk. *In silico* optimizations achieved velocity profile uniformity with coefficients of variance of 0.89% and 0.86% for the spine- and leaf-inspired designs, respectively. However, simulations revealed that velocity uniformity alone is insufficient for accurate molecular capture prediction without consistent reaction site channel dimensions. The bio-inspired designs demonstrated superior performance, stabilizing—coefficient of variance below 20%—in DNA capture within 10 minutes, compared to 68 minutes for a simple branched design. This work underscores the potential of bio-inspired microfluidics to enable scalable, uniform, and high-performance systems for multi-analyte detection.

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Introduction

Multiplexing, which refers to either generating multiple signals for a single analyte¹ or detecting multiple analytes simultaneously, plays a critical role in advancing diagnostics across various fields.² In health monitoring and disease diagnostics, the continuous multiplexed measurement of biomarkers such as glucose,³ lactate,³ urea,⁴ citrate,⁵ metal ions,⁶ and small proteins such as enzymes, hormones, and cytokines provides invaluable information about physiological health.⁷ Similarly, profiling microRNA (miRNA) biomarkers has gained prominence for diagnosing, assessing prognosis, and monitoring diseases, including cancer, neurodegenerative disorders, and cardiovascular conditions.^{8,9} Thousands of miRNAs are screened to obtain accurate profiles of pathogenic expressions, with focused panels typically requiring 20–42 analytes for precise diagnosis.⁸ In environmental and food safety monitoring, multiplexing is

required for the detection of well over 100 pathogens (*e.g.* bacteria¹⁰ and viruses¹¹), contaminants, and harmful chemicals¹⁰ in a single sample. Identification of different species, as well as determination of antibiotic resistance can inform effective treatment strategies and reduce response times, potentially saving lives.¹² These diverse biomarkers can be detected by immobilizing biorecognition elements such as aptamers,¹³ oligonucleotides, enzymes, antibodies, and peptides¹⁴ onto sensing surfaces designed to selectively bind to their targets.¹⁵ Integrating a large number of biosensors, often rely on the amalgamation of biorecognition elements into a single device which presents significant technical challenges, requiring multiple readout labels, cross-contamination, and signal interference.¹⁶

Conventional diagnostic methods that have been designed for operation at centralized laboratories are not suitable for rapid clinical decision making at or near the patient, which adds delays in diagnosis, especially for those in remote and resource-poor areas.^{17,18} This has fueled the development of portable, simple, rapid, and multiplexed point-of-care (POC) diagnostics.¹⁹

Microfluidic systems offer several advantages for the development of fully-integrated biosensors for POC diagnostics and health monitoring.⁷ These include reducing sample and reagent volumes,²⁰ increasing local analyte concentrations,²¹ enabling multiplexing,²² and providing reproducible reaction conditions at the detection zones,²³ all of which are essential for optimizing sensor performance.

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As demonstrated in previous studies, most multi-analyte microfluidic designs are constrained by the limited number of analytes they can effectively detect. To overcome this limitation, we developed biomimetic microfluidic systems inspired by the spinal cord and staghorn plant leaf vein networks, incorporating 38–42 biosensors into a single microfluidic system. These bio-inspired designs were optimized *in silico* to achieve uniform flow velocity and consistent analyte capture across different channels while maintaining spatial separation to prevent cross-talk between reaction sites. The performance of these designs was further validated through direct comparison with a simpler branched microfluidic design.

Methods

Theory

We simulated the fluid dynamics within the microfluidic channels using COMSOL Multiphysics® software (version 6.2, COMSOL AB, Stockholm, Sweden). To apply the computational finite element analysis from the hydrodynamic equations module, we assumed laminar flow of an incompressible fluid, governed by the Navier–Stokes eqn (1). This equation governs the motion of fluids, representing the conservation of momentum, where u is the velocity of fluid, ρ is the density of fluid, p is pressure, K is the viscous stress tensor, and F denotes the external force applied to the fluid. For incompressible flow, where the density remains constant, the continuity eqn (2) converges to

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strategy for laminar flow used the default fine mesh option. Additionally, we tested the chosen fine mesh under varies flow rates ($10\text{--}1000\ \mu\text{L min}^{-1}$), demonstrating no difference in the coefficient of variance measurement (Fig. S2†). In the 3D simulation, the meshing strategy was designed to achieve accurate results while maintaining computational efficiency. We employed a combination of physics-defined and user-defined approaches, utilizing a fine mesh for the reaction sites, a

fine mesh for the boundaries, and a coarse mesh for the remaining geometry. Further increase of mesh refinement showed no improvement in capture kinetics.

The fraction of free sites was obtained by using boundary probes that are assigned to measure the fractions of free sites at each of the reaction sites. The fractions are then converted into capture efficiency using eqn (9):

$$\text{Capture efficiency (\%)} = 100\% \times (1 - \text{fraction of free sites}) \quad (9)$$

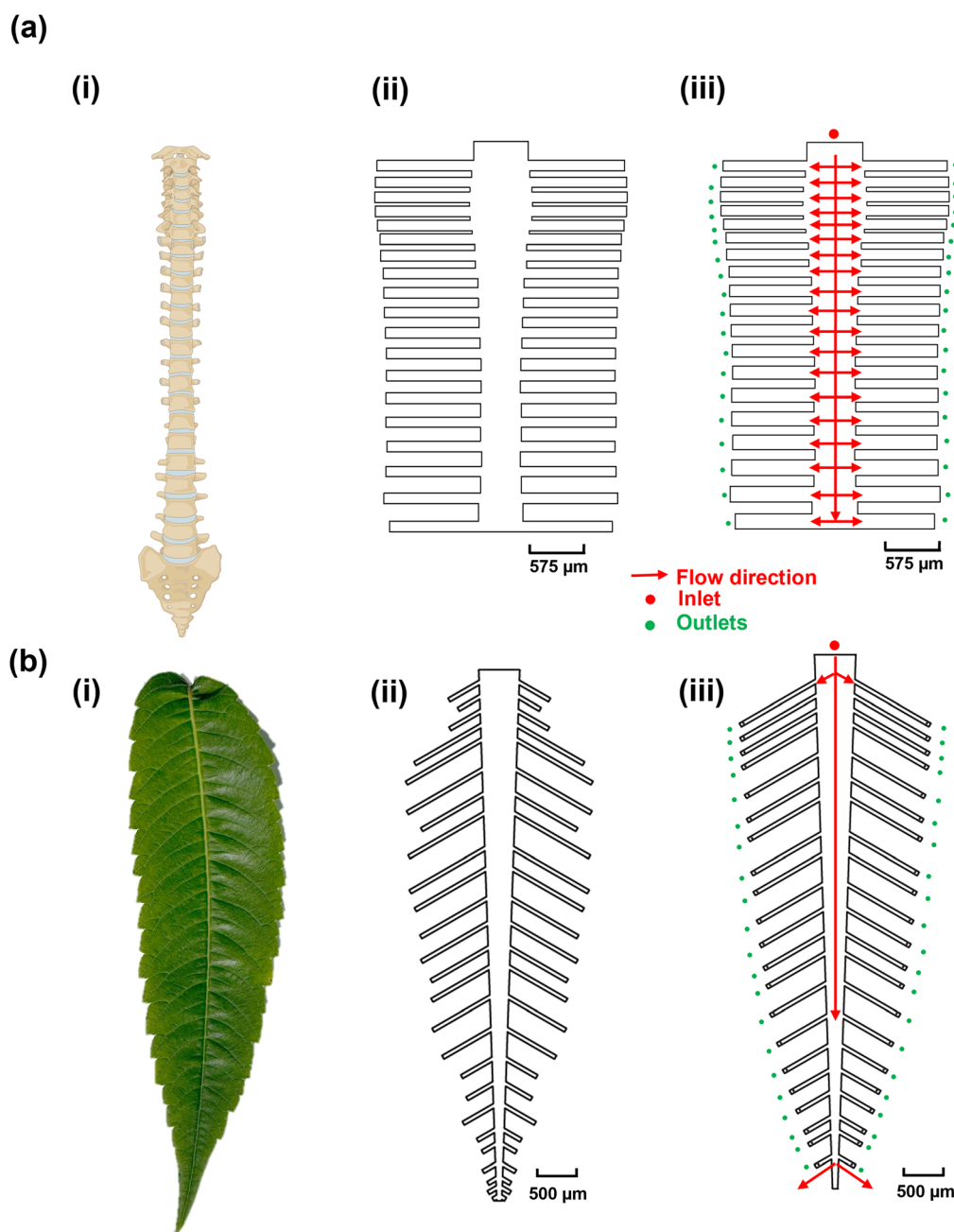


Fig. 1 Design of the bio-inspired multiplexed microfluidics. (a) Human spine-inspired design, (i) human spine schematic, (ii) the original scaled down design of a healthy human spinal vertebrae for microfluidics, (iii) the optimized design of the healthy human spinal vertebrae for microfluidics. (b) Staghorn sumac leaf-inspired design, (i) staghorn sumac leaf, (ii) the original scaled down design of the staghorn sumac leaf for microfluidics, (iii) the optimized design of the staghorn sumac leaf for microfluidics.



Design of bio-inspired microfluidic systems

Optimization of the spine-inspired microfluidics design

Optimization of the leaf-inspired microfluidics design

DNA–DNA hybridization uniformity in the bio-inspired designs

We sought to answer whether the optimized designs are in fact superior in DNA hybridization uniformity over the original designs, evaluated by calculating the variance in capture coefficient across the various reaction sites. In order to accurately simulate capture, a probe density of 4.55×10^{12} molecules per cm^2 , K_{on} of $0.96 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$, and K_{off} of 0.09 min^{-1} were extracted from previous work in a similar system,⁴⁶ resulting in a K_{d} of 94 nM. We then simulated the system (Fig. 4a) at a fully developed flow to mitigate initial operational effects (*e.g.* pump initial variability) with a gradual concentration increase from 0 nM to a homogenous target concentration of 100 nM—positioned at the middle of the log-linear dynamic range of the biosensor—to understand and verify the uniformity of the binding kinetics on the spine and leaf inspired systems. Circular electrodes were positioned at an equal distance from all the subchannel outlets, and they were modeled as reaction sites to capture the flowing target at flow rates of

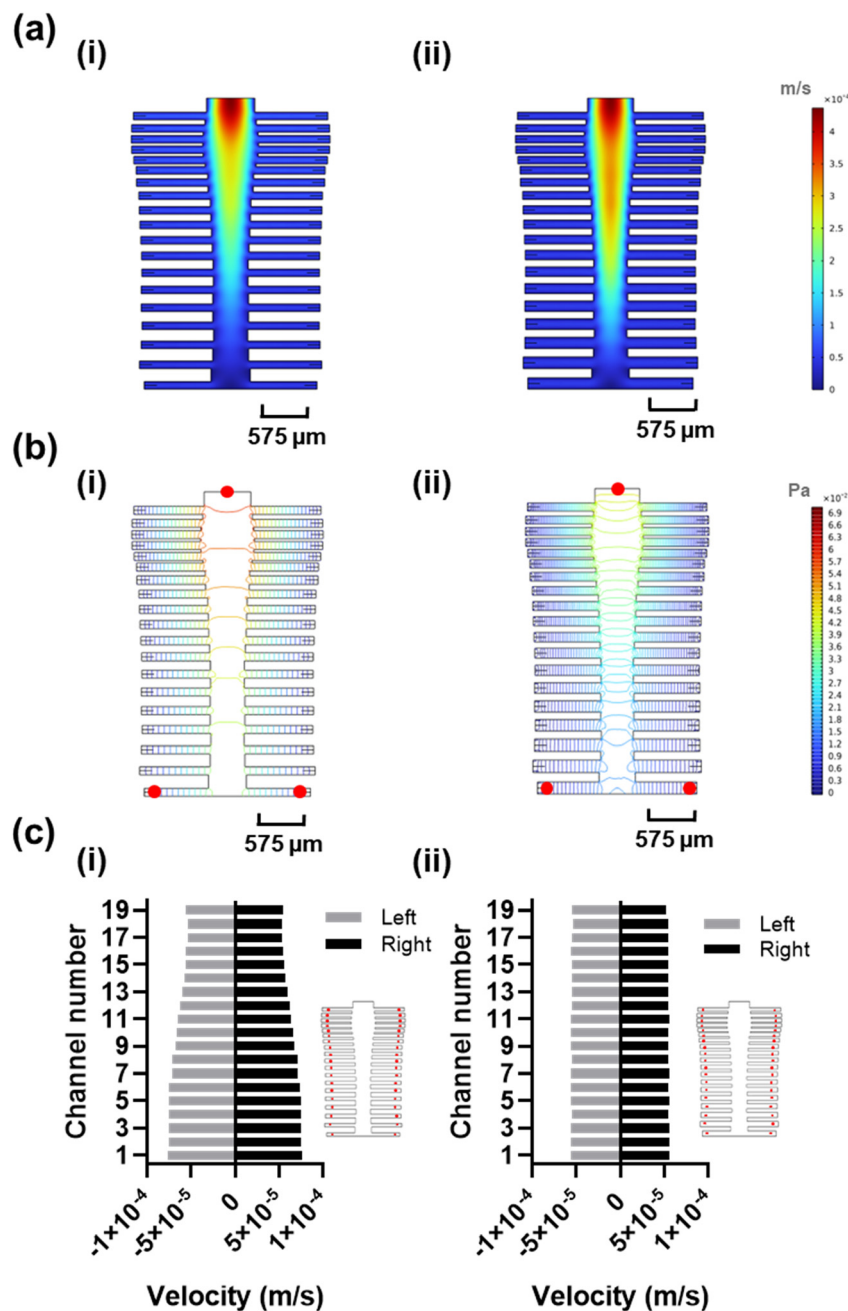


Fig. 2 Redesign of the spine-inspired design. (a) Velocity profile of the original (i) and optimized (ii) design. (b) Pressure profile of the original (i) and optimized (ii) design. (c) Velocity vector in each reaction site (red circles) for the original (i) and optimized (ii) design. Simulations are run using fully developed laminar flow at $100 \mu\text{L min}^{-1}$ flow rate.

10, 50 and $100 \mu\text{L min}^{-1}$. As the concentration of target is higher in the bulk solution than the reaction sites, molecules diffuse from the bulk to the reaction sites through the diffusion layer⁵⁴ (Fig. 4b). We expect the capture efficiency of the reaction sites within different subchannels to be the same because of the reduced coefficient of variance of the velocity vector at the reaction sites (Fig. 2c-ii and 3c-ii), which ensures uniform convection and target transport. However, coupling convection, diffusion, and surface reactions in the simulation of capture

efficiency will achieve a more accurate prediction than convection alone of the performance of the bio-inspired designs for biosensing.

The original and optimized spine-inspired designs show the same capture efficiency over time in all the 38 capture reaction sites and minimal drop in hybridization efficiency between the reaction sites in the first and last channels (Fig. 4c and d), with a coefficient of variance of 0.43% and 0.59% at $100 \mu\text{L min}^{-1}$, 1.14% and 1.49% at $50 \mu\text{L min}^{-1}$, and 3.20% and 3.61% at $10 \mu\text{L min}^{-1}$ for the original and



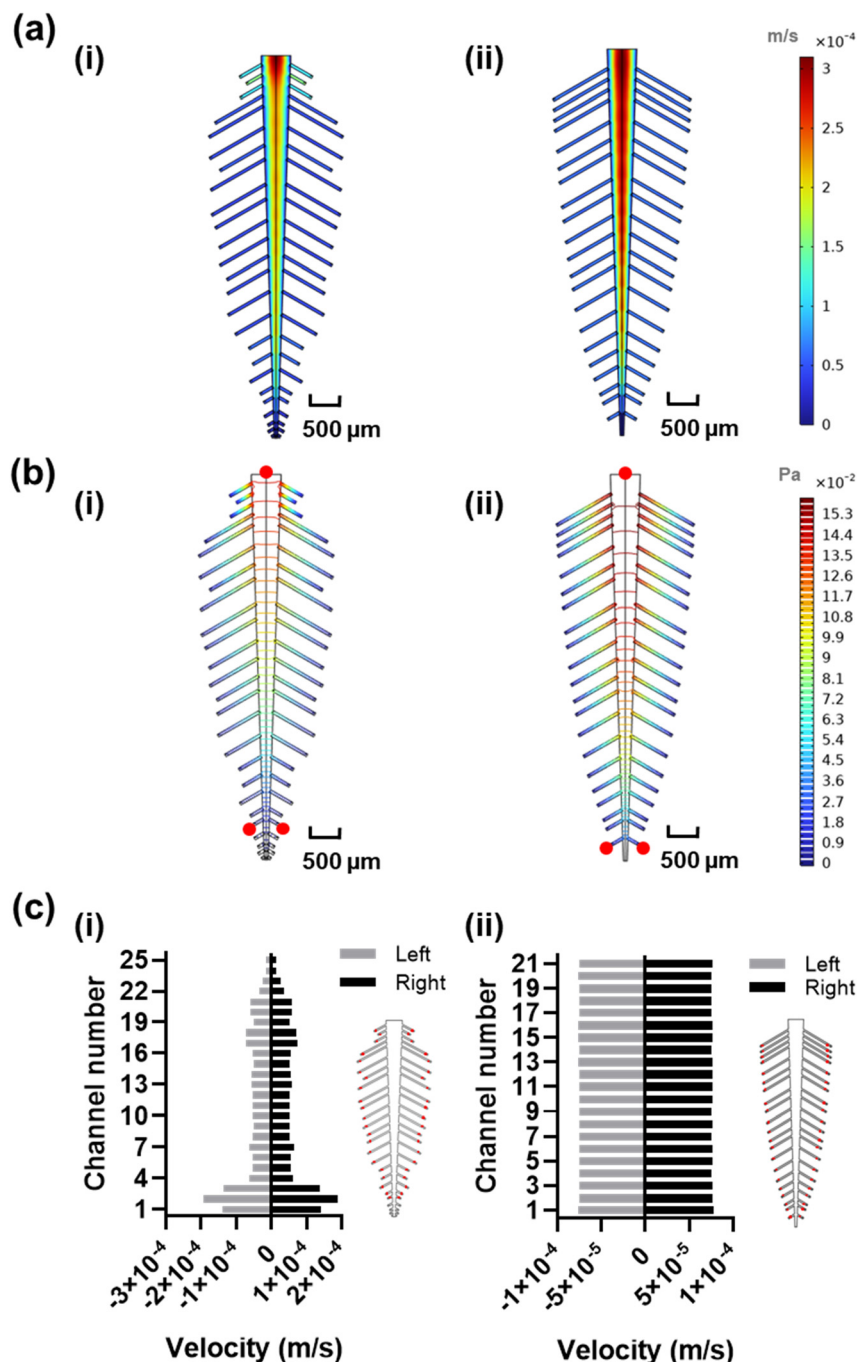


Fig. 3 Redesign of the leaf-inspired design. a) Velocity profile of the original (i) and optimized (ii) design. b) Pressure profile of the original (i) and optimized (ii) design. c) Velocity vector in each reaction site (red circles) for the original (i) and optimized (ii) design. Simulations are run using fully developed laminar flow at $100 \mu\text{L min}^{-1}$.

optimized spine-inspired designs at 20 minutes, respectively (Fig. S4a†). While both original and optimized spine-inspired designs demonstrate uniform capture across all 38 subchannels, it is interesting to observe that the original spine-inspired design has marginally lower coefficient of variance in all the tested flow rates ($10, 50, 100 \mu\text{L min}^{-1}$) (Fig. S4a†). We hypothesize that the optimized spine-inspired design is more variable due to variable widths (ranging from $98.5\text{--}153.5 \mu\text{m}$) of the subchannels, creating variable amount

of target diffused DNA within each subchannel.⁵⁵ While in the original spine-inspired design with uniform subchannels widths ($100 \mu\text{m}$), the distance between the centerline of the flow and the reaction sites (diffusion path) is equal, allowing target DNA to reach the reaction site uniformly through sideways (lateral) diffusion.⁵⁴ Furthermore, as flow rate increases, convection becomes more dominant, reducing the effect of diffusion, resulting in less difference between the original and optimized spine-inspired systems (Fig. S4a†). At



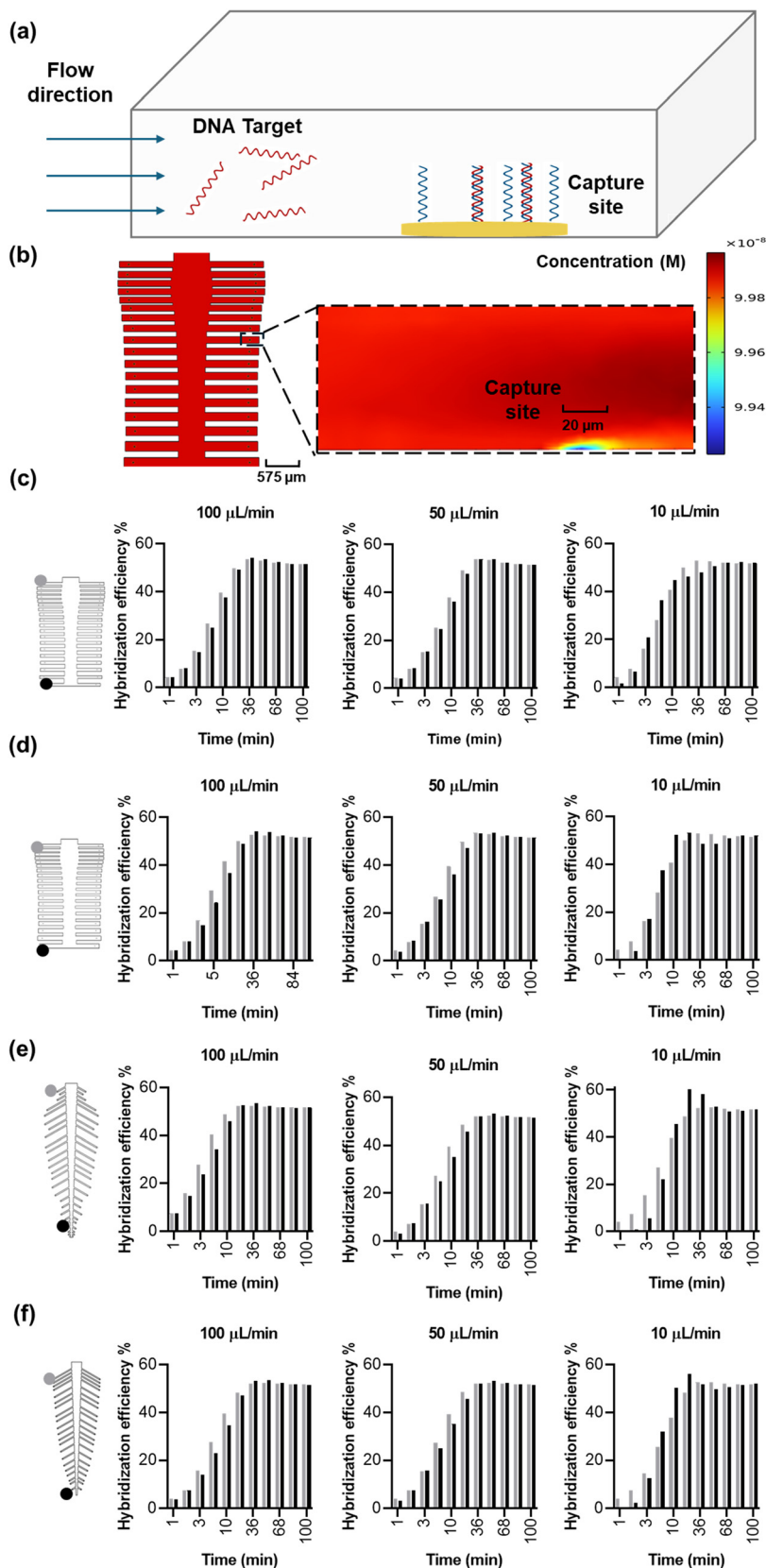


Fig. 4 DNA–DNA hybridization of the bio-inspired designs. (a) Schematics of the flowing DNA target and capture at the reaction/capture site using single stranded DNA probes. (b) Simulated channel cross section, showing the bulk target concentration of 100 nM and a reaction site. Hybridization efficiency of the original (c) and optimized (d) spine designs for the first (gray) and last (black) reaction sites. Hybridization efficiency of the original (e) and optimized (f) leaf designs for the first (gray) and last (black) reaction sites. Simulated laminar flow was set for a target concentration of 100 nM under a range of flow rates (10, 50, and 100 $\mu\text{L min}^{-1}$).



flow rates of 10, 50, and 100 $\mu\text{L min}^{-1}$, the average Peclet numbers for the original design are 0.62, 3.09, and 6.19,

compared to 0.53, 2.63, and 5.26 for the optimized design, confirming the dominance of diffusion at lower flow rates.

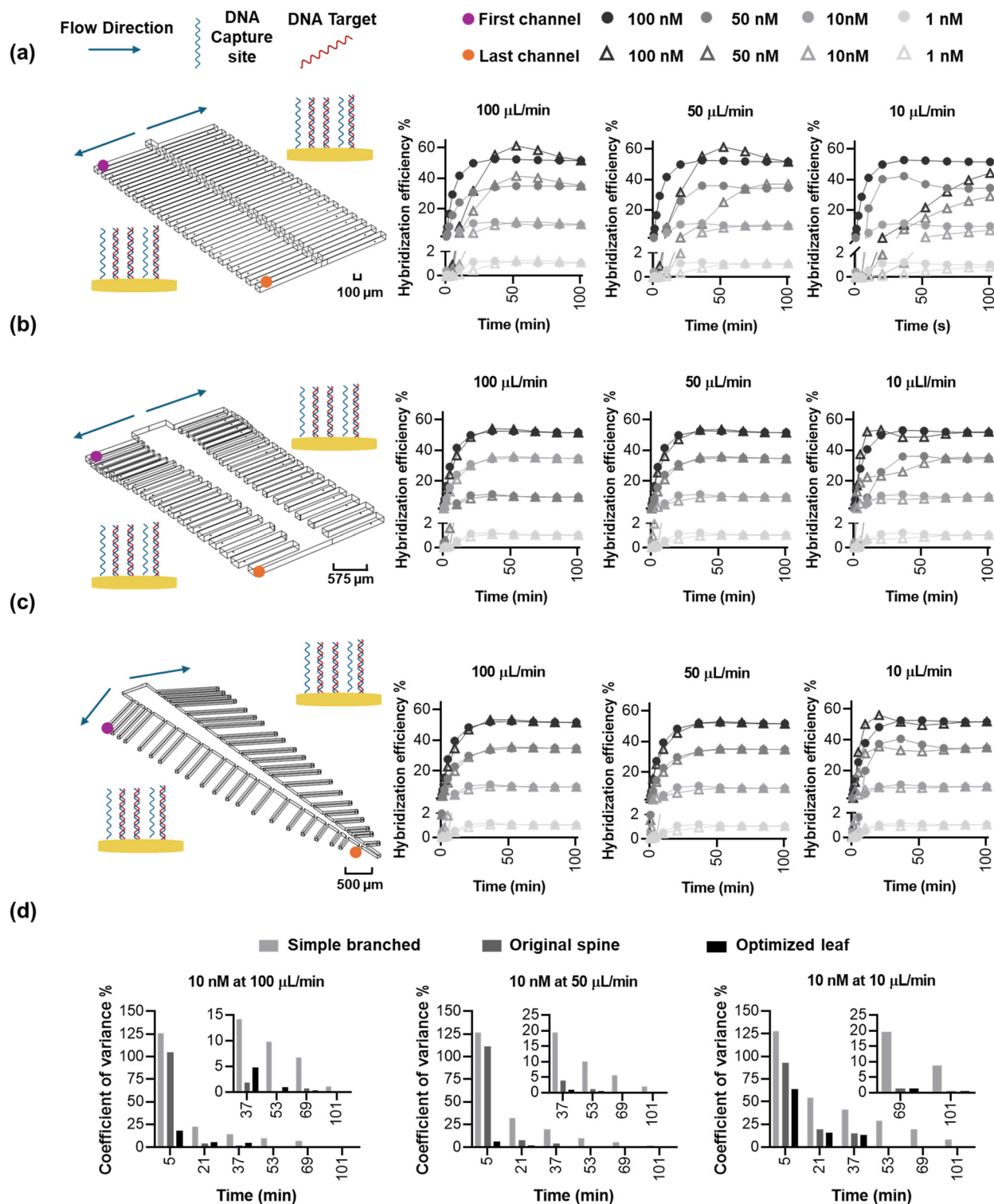


Fig. 5 Comparison of DNA-DNA hybridization kinetics of a simple branched design and the bio-inspired designs. The schematic and the hybridization efficiency at the first (purple) and last (orange) reaction sites for the simple branched (a), original spine-inspired (b), and optimized leaf-inspired (c) designs, along with a coefficient of variance analysis (d) across all the reaction sites for a target concentration of 10 nM at 100 $\mu\text{L min}^{-1}$ flow rate for the simple branched, original spine-inspired, and optimized leaf-inspired designs. Insets in (d) demonstrate rescaled y-axis versus time. Results show various DNA target concentrations (1, 10, 50, 100 nM), under a range of flow rates (10, 50, 100 $\mu\text{L min}^{-1}$).



The original and optimized leaf-inspired designs demonstrate uniform capture efficiency over time with the optimized design being less time variable and demonstrating a smaller drop in hybridization efficiency between the reaction sites in the first and last channels (Fig. 4e and f). These designs exhibit coefficient of variance of 1.5% and 0.79% at $100 \mu\text{L min}^{-1}$, 1.74% and 1.74% at $50 \mu\text{L min}^{-1}$, and 8.33% and 5.49% at $10 \mu\text{L min}^{-1}$, for the original and optimized leaf-inspired designs at 20 minutes, respectively (Fig. S4b†). The improved variability in the optimized leaf-design is expected due to the uniform widths ($80 \mu\text{m}$) of all the subchannels in both leaf-inspired designs. A clear trend is observed in all the original and optimized designs (Fig. 4c–f), demonstrating initial high variability due to analyte concentration gradient across the microchannels. As the transport of analytes and reactions progress, moderate variability arises as convection–diffusion redistributes analytes downstream, eventually reaching a plateau as the system equilibrates. At lower flow rates ($10 \mu\text{L min}^{-1}$), diffusion dominates, causing slower equilibration (68 minutes). In contrast, higher flow rates (50 – $100 \mu\text{L min}^{-1}$) enhance convection, reducing variability and allowing faster equilibrium (36 minutes).

Leveraging velocity profile geometry and surface reactions modeling is an effective approach for enhancing DNA–DNA hybridization uniformity in biosensor designs. Based on the uniformity of DNA–DNA hybridization, we selected the original spine-inspired design and the optimized leaf-inspired design for further kinetic analysis.

To understand whether a bio-inspired branched design is indeed needed for multiplexed biosensing, we compared the performance of the spine- and leaf-based designs to a simple branched channel with the same main and subchannels width ($100 \mu\text{m}$) containing a similar number (40 electrodes) of reaction sites (Fig. 5a). The simple branched design demonstrated a velocity coefficient of variance of 210.98% at the 40 reaction sites (Fig. S5†). Our simulation of DNA–DNA kinetics – simulated with a surface coverage 4.55×10^{12} molecules per cm^2 , range of target concentration (1, 10, 50, and 100 nM), and under variable flow rates (10, 50, $100 \mu\text{L min}^{-1}$), resulted in a large drop of hybridization efficiency between the first and last channel reaction sites in the simple branched compared to the spine and leaf inspired designs (Fig. 5a–c). Additionally, the systems demonstrate a trend of high ($>35\%$) at 36 minutes for the simple branched and 5 minutes for the bio-inspired designs, moderate (10–35%) at 84 and 36 minutes for the simple branched and bio-inspired designs, respectively, and low ($<10\%$) coefficient of variance overtime for both designs across all target concentration and flow rate parameters (Fig. 5c, Tables S4–S6†). The highest variability demonstrated by all three designs is at target 10 nM under $10 \mu\text{L min}^{-1}$ showing a coefficient of variance of 127.81%, 92.58%, and 63.64% at 5 minutes, 54.14%, 19.24%, and 16.05% at 20 minutes, 29.23%, 5.48%, and 5.79% at 52 minutes, and 8.68%, 0.49%, and 0.52% at 100 minutes for the simple branched, spine-inspired, and leaf-inspired

designs, respectively. Less variability at later timepoints is reported in literature when surface reaction and mass transport models are taken into account.⁵⁶ Interestingly, the DNA capture coefficient of variance decreases with the increase of flow rate from 10 to $100 \mu\text{L min}^{-1}$ (Fig. 5d), respectively, which could be attributed to the dominance of convection over diffusion at higher flow rates, ensuring more uniform delivery of target DNA molecules to the reaction sites.⁵⁷ While a simple branched design may be appropriate in specific cases where a capture gradient is beneficial,⁵⁸ its significant variability in molecular capture across reaction sites, extending up to 68 minutes, makes it unsuitable for applications requiring rapid and uniform multi-analyte detection.

The bio-inspired designs were further evaluated under different surface probe densities (low: 4.55×10^{11} , high: 4.55×10^{13} molecules per cm^2) at a target concentration of 100 nM under $100 \mu\text{L min}^{-1}$ flow rate. Although higher probe densities resulted in slightly increased variability in the leaf-inspired design, both spine- and leaf-inspired designs maintained a coefficient of variance below 5% across all time points (1–164 minutes, Fig. S6, Table S7†). Furthermore, the bio-inspired designs were tested using various fluids characterizing different specimens used in clinical biosensing (plasma, whole blood, and saliva) using a moderate probe density of 4.55×10^{12} molecules per cm^2 and a target concentration of 100 nM under a flow rate of $100 \mu\text{L min}^{-1}$. The experiments resulted in a more pronounced effect than varying the probe density, with saliva showing the highest variability, followed by blood and plasma, corresponding directly to their viscosities from high to low (Table S1†). Higher viscosity reduces the diffusion coefficient, slowing the random motion of molecules and increasing the time needed for them to reach the reaction sites.⁵⁹ As a result, dilution may be necessary for whole blood and saliva, particularly when using short incubation times (<10 minutes in the original spine-inspired design and <20 minutes in the optimized leaf-inspired design). In all complex media the original spine-inspired design achieved variability below 10% within 1 minute, while the optimized leaf design required 20 minutes to reach similar variability levels (Fig. S7, Table S8†). This highlights the superior performance of bio-inspired designs in challenging media, where uniformity and rapid response are critical.

Conclusion

There is a growing need for multiplexed biosensors that ensure uniform flow velocity, analyte distribution, and target capture for high-throughput multi-analyte detection. To address this, we adapted the designs of the spinal cord and leaf vein networks into microfluidic platforms, leveraging their inherent self-regulation and optimized resource distribution. These bio-inspired structures aim to achieve uniform flow and DNA–DNA hybridization, providing a robust foundation for multiplexed detection systems.



To evaluate the efficacy of these designs, we first analyzed the velocity and pressure profiles in the original designs, followed by optimizing their dimensions to improve flow uniformity at the reaction sites through computational simulations. We then compared the original and optimized designs in terms of molecular capture at a target concentration of 100 nM, under varying flow rates (10, 50, and 100 $\mu\text{L min}^{-1}$). Notably, the original spine-inspired design exhibited less variability than the optimized design, suggesting that a combined approach—optimizing flow dynamics, mass transport, and surface reaction modeling—better predicts DNA capture uniformity than flow dynamics alone.

In further validation, we compared a simple branched design with the bio-inspired designs to assess the variability in target capture in the different reaction sites. The capture kinetics in both designs initially exhibited high variability more than 35% at 36 minutes for the simple branched and 5 minutes for the bio-inspired designs, transitioning to moderate variability between 10% and 35% at 84 and 36 minutes for the simple branched and bio-inspired designs respectively, then eventually both designs stabilizing with less than 10% variability as adsorption–desorption and mass transport reached steady-state. Notably, the bio-inspired designs demonstrated significantly lower variability compared to the simple branched design, achieving stabilization (coefficient of variance <20%) within 10 minutes, compared to up to 68 minutes for the simple branched design under varying flow rates and target concentrations. Furthermore, the bio-inspired systems were tested using various probe densities and complex media (plasma, whole blood, and saliva), demonstrating low variability across all conditions, highlighting the benefits of bio-inspired designs for biosensing.

The findings underscore the advantages of bio-inspired methodologies in the creation of multiplexed and multi-analyte sensing devices. We anticipate that these designs will find practical applications in areas requiring multiplexing, such as organ-on-a-chip platforms, monitoring food and water for various contaminants, and diagnostic panels. Future research will concentrate on refining these designs through experimental validation to develop optimized multiplexed systems for the aforementioned applications.

Data availability

The data supporting this article have been included as part of the ESI†

Author contributions

E. O. designed the study, conducted the simulation, data analysis, and manuscript writing. J. L. H. contributed to the surface reactions simulations and manuscript writing. P. L. contributed to design optimizations and manuscript editing. L. S. contributed to the design and conceptualization of the

study and manuscript writing. All authors have approved the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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