COMPOSABLE SYSTEM SIMULATION OF DISPERSION IN COMPLEX ELECTROPHORETIC SEPARATION MICROCHIPS

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ABSTRACT

This paper presents a composable system simulation framework for electrophoretic separation microchips, using an analog hardware description language integrating analytical dispersion models that describe not only the behavior of individual components, but also the interactions between them. Both DC and transient analysis are performed in the framework. The accuracy (relative error less than 10%) and tremendous speedup (100~10,000×) of composable system simulations are verified by comparison to experiment and numerical studies.

Keywords: dispersion, system simulation, electrophoretic separation microchips

1 INTRODUCTION

While electrophoretic separation microchips have been widely studied in the past decade, their efficient simulation and design at the system-level continues to be a challenge. Experimental trial-and-error and numerical computation methods can lead to unacceptably long design cycles. Several analytical [1, 2] and semi-analytical [3] models and simulations of analyte band broadening (dispersion) have been proposed to speed up design at the component-level. A system simulation approach in which a design is decomposed into components has been presented [4], but involves over-simplified dispersion models that do not accurately account for component interactions and still require users with expert knowledge. To address these issues, this paper presents a composable system simulation framework using an analog hardware description language (Verilog-A) integrating analytical dispersion models [5] that are capable of capturing the interactions between components. The simulations illustrate the effect of chip topology, analyte properties and buffer properties on separation performance. Thus, it is generally applicable to the design of practical electrophoretic microchip devices.

2 COMPOSABLE SYSTEM SIMULATION

Our composable simulation framework consists of a model library and simulation engine. One major contribution over [5] is the development of a Verilog-A library consisting of parameterized behavioral models for commonly used components in separation microchips. Users can compose a complex design schematic by wiring these blocks for a fast and reliable top-down iterative approach to system-level design. Figure 1 illustrates two practical electrophoresis systems (serpentine and spiral) and their schematics. The systems are decomposed into a set of components including reservoirs, detector, injector, straight channels and turns, which are then linked via interface parameters according to the spatial layout and physics. Cadence is used to netlist the structure of the composable network and Spectre is employed as the simulator in this paper as in [6] (other schematic editors and simulators capable of simulating Verilog-A can also be used).

2.1 Interface parameters

The first step in creating a composable model of a system is to identify the parameters that will be communicated between neighboring components (interface parameters). There are two kinds of interface parameters involved in the network. One is the nodal voltage globally determined by Ohm’s and Kirchhoff’s laws. The other pertains to dispersion and includes variance (σ²), the longitudinal standard deviation of the cross-sectional average concentration; skew coefficients (B_m), used to
describe the skew caused by the turns; separation time \( t \), the moment the center of mass of the band reaches the component; and amplitude \( A \), the maximum concentration. Since the dispersion occurring in the downstream component doesn’t affect the upstream, the parameters related to dispersion are calculated using a directional signal flow in which the output from one component is assigned as the input to the next, starting from an injector.

### 2.2 Behavioral Models

After selecting the interface parameters, the second step in developing a composable model library is selecting the list of composable elements, and deriving behavioral models for each element. Our composable library consists of seven basic models, which include turns (90° or 180°, clockwise or counter-clockwise), straight channel, injector and detector. The goal of each behavioral model is to capture the input-output signal flow relationship between the dispersion interface parameters and the equivalent Kirchhoffian electric network for the voltage interface parameter (see Figure 2). In a simulation scheme, the steady nodal voltage and the electric field through the component will be determined first. Users only need to input the voltages applied on all reservoirs as boundary conditions, and the simulator is able to calculate the voltages on the nodal points. Based on these points, the transient analysis is initiated and detected.

The residence time and amplitude ratio through a component is given as

\[
A_{in}/A_{out} = \sqrt{\sigma_{in}^2/\sigma_{out}^2}
\]

where \( A \) is the electrophoretic mobility of the species, \( L \) is the longitudinal length of the component; for a turn, \( L = \theta R_c \), and \( \theta \) is the angle of the turn. To obtain Eq (2), we always assume a Gaussian concentration distribution for the analyte band in the system.

\[
\Delta t = L/E \mu \quad \text{and} \quad A_{out}/A_{in} = \sqrt{\sigma_{in}^2/\sigma_{out}^2}
\]

where \( \mu \) is the electrophoretic mobility of the species, \( L \) is the longitudinal length of the component; for a turn, \( L = \theta R_c \) and \( \theta \) is the angle of the turn. To obtain Eq (2), we always assume a Gaussian concentration distribution for the analyte band in the system.

\[
B_{m, out} = B_{m, in} \cdot e^{-(m \pi^2) \Delta D/j \omega^2}
\]

\[
\Delta \sigma^2 = 2D \cdot \Delta t
\]

\[
\Delta \sigma^2 = 2D \Delta t \pm 8 w^4 \theta \sum_{m=0}^{\infty} \frac{B_{m, in} \left(1 - e^{-\pi^2 D \Delta t/j \omega^2}\right)}{(m \pi)^4} + 64 w^6 \theta^2 \sum_{m=0}^{\infty} \frac{-1 + e^{-\pi^2 D \Delta t/j \omega^2} + (m \pi)^2 D \Delta t/j \omega^2}{(m \pi)^8}
\]

\[
C_m = A_{out} \cdot e^{-(E \mu)^2 (t-t_\text{out})^2/2 \sigma_{out}^2}
\]

where \( A_{out} \), \( t_\text{out} \) and \( \sigma_{out}^2 \) are detector outputs from DC analysis; \( t \) is the actual read-out time.

### 3 RESULTS AND DISCUSSION

Our composable system simulation results are shown in Figures 3-6. In Figure 3A, an electrophoresis column of two complimentary turns used to separate TRITC-Arg is
compared to our DC system simulations, showing excellent agreement. According to [5], the final variance normalized by \( w^2 \) depends on two dimensionless times \( \tau_t \) and \( \tau_s \), the ratio of the time for an analyte molecule to advect through a channel to the time for it to diffuse across the channel width (\( \tau = \Delta t D/w^2 \), \( \tau_t \) is the dimensionless time in the turn and \( \tau_s \) in the inter-turn straight channel). In this simulation, \( \tau_t = 0.068 \) is relatively small, and transverse diffusion in the turn does not have enough time to remove all of the turn-induced skew, which accordingly incurs abrupt increase in variance (see the skewed band after the first turn in the numerical simulation plot in Figure 3A). During an analyte’s migration in the long inter-turn straight channel, the transverse diffusion has adequate time (relatively high \( \tau_s = 0.696 \)) to smear out most of the skew and presents a nearly uniform band before the second turn. The second turn then distorts the band again in the opposite direction, leading to another turn-induced variance equal to the one caused by the first turn. Figure 3B shows electropherograms from three detectors placed in the system. Respectively their positions are before the first turn, in the inter-turn straight channel, and after the second turn. Since both turns broaden the analyte band, the amplitude decreases consecutively and the band spreads out, where an initial band with variance \( \sigma^2 = 100 \ \mu m^2 \) and normalized amplitude \( A = 1 \) was injected.

\[
\tau_t = 0.068 \quad \text{and} \quad \tau_s = 0.696
\]

\[
\sigma^2 = 100 \ \mu m^2
\]

\[
A = 1
\]

\[
\Delta t D = 3.12 \times 10^{-10} \ \text{m}^2/\text{s}
\]

\[
w = 50 \ \text{mm}
\]

In Figure 4, numerical and composable simulations are conducted, in which all parameters in Figure 3 are kept unchanged except for a very low diffusivity (common for DNA sequencing in gels or matrix materials), rendering extremely low \( \tau_t = 2.2 \times 10^{-3} \) and \( \tau_s = 2.23 \times 10^{-2} \). A maximum relative error of 5.6% is found. Netlisting and DC simulation take 50 seconds for the first time, and less than a second for subsequent iterations, leading to a 150~7,500× speedup. In this example, the longitudinal molecular diffusion is very small, inferred by the nearly zero change of variance in the straight channel; and the convection is significant in the total dispersion. Hence the analyte band keeps its sharp skew before arriving at the second turn that corrects most of the skew and leads to a reduced final variance. This indicates the importance of individual system level simulation and design for different species analysis. The transient simulation shows different concentration read-outs of the three detectors, compared to Figure 3B. Due to less dispersion of the analyte band, all detectors in Figure 4B show better performance compared to Figure 3B, as seen by the higher concentration output in Figure 4B. Because of the skew correction and dispersion reduction by the 2nd turn, the detector after the second turn shows a higher peak and narrower band than that in the inter-turn straight channel. This shows that for the microchip electrophoresis of low-diffusivity species, e.g.
the DNA in gels or other matrix materials that further reduce the diffusion coefficient, even numbers of turns should be applied to take advantage of the skew canceling interactions caused by complimentary turn pairs.

In Figure 5, a serpentine electrophoretic separation system (similar to Figure 1) involving six complimentary turns is simulated and compared to numerical results. The variance growth at the outlets of the second, the forth and the sixth turn are extracted. A worst-case error of 9.5% at the lowest $\tau_s$ and $\tau_t$, and a 600~15,000× speedup are obtained. An observation can be made here that the variance increases with the even number of complimentary turns in a superlinear to sublinear manner depending on $\tau_s$ and $\tau_t$ [9].

In Figure 6, a complex spiral separation microchip of five turns to separate Dichlorofluorescein is simulated and compared to experimental results. A worst-case error of 12% on plate number is found. The linear growth of plate number with electric field confirms that molecular diffusion is the major dispersion source in such a system [10].

4 CONCLUSION

A composable system simulation framework for complex electrophoretic separation microchips has been presented, in which a parameterized behavioral model library using an analog hardware description language (Verilog-A) has been developed. Kirchhoff’s law and directional signal flow have been employed to solve the electric and dispersion network respectively. The system simulation results have been verified by numerical and experimental data. The proposed interface parameters and behavioral models are able to accurately capture the combined effects of system topology and parameters (such as analyze and buffer properties) on the separation performance. The transient analysis is also conducted to intuitively observe the actual detector read-out of the cross-sectional average concentration. Compared to numerical methods, a tremendous speedup (100~10,000×) can be achieved by the composable simulation, while still maintaining high accuracy (relative error less than 10%). This enables the sub-hour system-level synthesis and optimal design of electrophoretic separation microchips [11].

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