Novel Nano-Machine Architecture for Machine Learning in the IoBNT

Stefan Angerbauer 1, Franz Enzenhofer 1, Werner Haselmayr 1, and Tobias Pankratz 1

1Affiliation not available

October 31, 2023

Abstract

In this work, we propose a novel nano-scale architecture that performs matrix multiplications. Matrix multiplications are the basic operations of machine learning (ML) algorithms and, thus, the presented approach enables their application at the nano-scale, for example inside the human body in the Internet of Bio-Nano-Things (IoBNT). It is based on the molecule exchange between connected compartments and introducing chemical reactions in some of them. The matrix entries are solely defined by the volumes of the compartment. We provide a detailed mathematical description of the stochastic and dynamic behavior of the system. Moreover, we derive design guidelines for the proposed architecture. Finally, we validated the proposed approach through particle-based simulations.
Novel Nano-Machine Architecture for Machine Learning in the IoBNT

Stefan Angerbauer*, Tobias Pankratz†, Franz Enzenhofer†, and Werner Haselmayr‡

*Institute for Communications Engineering and RF Systems, JLU LIT SAL eSPML Lab, Johannes Kepler University (JKU), Austria
†Institute for Communications Engineering and RF Systems, Johannes Kepler University (JKU), Austria
‡Institute for Communications Engineering and RF Systems, Johannes Kepler University (JKU), Austria

Email: stefan.angerbauer@jku.at, tobias.pankratz@jku.at, franz.enzenhofer@jku.at, werner.haselmayr@jku.at

Abstract—In this work, we propose a novel nano-scale architecture that performs matrix multiplications. Matrix multiplications are the basic operations of machine learning (ML) algorithms and, thus, the presented approach enables their application at the nano-scale, for example inside the human body in the Internet of Bio-Nano-Things (IoBNT). It is based on the molecule exchange between connected compartments and introducing chemical reactions in some of them. The matrix entries are solely defined by the volumes of the compartment. We provide a detailed mathematical description of the stochastic and dynamic behavior of the system. Moreover, we derive design guidelines for the proposed architecture. Finally, we validated the proposed approach through particle-based simulations.

Index Terms—Molecular Communications, Molecular Machine Learning, Internet of Bio-Nano-Things (IoBNT)

I. INTRODUCTION

Machine Learning (ML) has gained tremendous attention from academia, industry and media due to its broad applicability and superior performance on various tasks. The applications of this technology span a wide variety of tasks, such as pattern recognition, time-series forecasting and natural language processing. The basis that unifies almost all ML algorithms is data. This is one particular reason, why this technology fits perfectly into the concept of the Internet of Everything (IoE) [1], [2], which aims to connect things and people to the internet. On the one hand, the IoE needs ML algorithms to process the huge amounts of data generated by its entities and on the other hand ML algorithms need this amounts of data to train their underlying models. However, for one sub-domain of the IoE, the Internet of Bio-Nano-Things (IoBNT) [3], [4], it is especially challenging to benefit from the possibilities opened up by ML. The IoBNT aims to connect Bio Nano-Things (BNTs) to the internet, which may lead to novel applications in medical diagnostics and health monitoring. BNTs are tiny machines that are capable of carrying out specific tasks, such as sensing the environment. They can be realized using either nano-technology or synthetic biology [5]. However, due to the small size of the BNTs, their computational capabilities are limited, which at first glance seems contrary to the computationally heavy paradigm of ML. Nevertheless, researchers explored different unconventional approaches to design nano-scale systems, that are capable of executing ML algorithms†. One of these approaches is based on genetic engineering of living cells. In [6], a synthetic genetic circuit was designed to work as a neuro-synapse in an E. coli bacterium. This artificial neuro-synapse, also called bactoneuron, forms a weighted linear combination of chemical input signals and converts them non-linearly into a fluorescent protein output, which corresponds to a single layer neural network (NN). The bactoneuron was experimentally validated using various computing tasks. However, the implementation of this concept is quite complex, since it requires genetic engineering and living cells. Another approach to realize nano-scale NNs is presented in [7]. Instead of engineering a synthetic circuit from scratch, gene regulatory networks are used, which are already naturally present in biological cells. In this approach, the main task is to find a sub-network of the gene regulatory network with the same structure as an artificial NN. Then the network weights are adjusted by setting gene expression rates via environmental conditions, such as temperature. However, this is not a trivial task, since the weights cannot be chosen independently from each other and, thus, realizing a generic NN based on this approach is very challenging. In [8], a chemical computation concept is presented, which does not rely on living cells. In particular, molecules propagate in microfluidic modules and depending on the module structure and the chemical reaction that takes place, different logic gates (e.g., AND gate) can be mimicked. Compared to [6], [7], this approach is technically easier to realize, since it is based on non-living chemical reactions. However, to implement ML algorithms a large number of logic gates would be required, which may limit the ability to down-scale to the nano-domain.

In this work, we introduce a novel nano-machine architecture that performs a matrix multiplication and, thus, builds the basic operation for ML algorithms‡. Similar to [8], the presented approach does not require living cells, but in contrast to [8], the novel architecture allows an efficient implementation of ML algorithms in the micro- and nano-domain. The principle is based on the propagation of molecules between connected compartments, with chemical reactions taking place

†The majority of these algorithms refer to neural networks (NNs), a specific type of ML algorithms.
‡The actual implementation of ML algorithms based on the proposed architecture is left for future work.
in some compartments. The entries of the matrix can be chosen independently only by adjusting the volume of the compartments. The contributions of this work can be summarized as follows:

- We present a novel nano-machine architecture that enables matrix multiplications
- We provide a mathematical characterization of the proposed system, including its stochastic and dynamic behavior
- We verify the proposed architecture using particle-based simulations

II. BASIC PRINCIPLE

In this section, we first introduce the proposed system architecture and the used notation. Then, we provide a detailed description of the working principle. Finally, we derive a stochastic model of the system and discuss possible choices for the compartment volumes.

A. System Architecture

The architecture of a $2 \times 2$ matrix multiplication unit is depicted in Fig. 1. This structure is capable of multiplying the molecule concentration of the inlet compartments (input vector) with a user-defined matrix and the result corresponds to the concentration in the outlet compartments (output vector). Throughout this work, a compartment is a physical entity that has a well-defined volume and content, which is typically water with dissolved signaling molecules. In Fig. 1 the compartments are indicated by circles, with inlet, intermediate, and outlet compartments at the top, middle, and bottom, respectively. The compartments are connected by channels, represented through lines in Fig. 1. Each channel has the same dimensions, with length $L$ and cross-section area $S$. We assume two types of signaling molecules, denoted by A and B. These molecules are assumed to be able to pass the channels in the directions indicated by the arrows on the left and right side of Fig. 1. The molecules are linked by the irreversible chemical reaction with a third species C, that serves as a reaction partner to A and can only be found in the intermediates. We denote this reaction by

$$A + C \rightarrow B.$$  \hspace{1cm} (1)

It is important to note that we assume that the amount of C molecules is much larger than that of the A molecules. For this case, we can neglect the C molecules and model this reaction as first order reaction.

B. Notation

We denote the volume of the $i$-th inlet and $j$-th outlet by $V_{in,i}$ and $V_{out,j}$, respectively. Moreover, all outlets have the same volume given by $V_{out,j} = V$. For the intermediate volumes we use the notation $V_{i,j}$, which means that they connect the $i$-th inlet with the $j$-th outlet. Please note that inlets and outlets can only hold type A and B molecules, while the intermediate compartments can hold both molecule types. For the number of molecules $N(t)$ and the concentration $c(t)$ in a certain compartment we use a similar notation as for the volumes, with the addition of the molecule type in the superscript. For example, the number of molecules and the concentration in the $i$-th inlet is denoted by $N_{in,i}(t)$ and $c_{in,i}^{A}(t)$, respectively. Moreover, throughout this work the concentration is defined by $c(t) = N(t)/V$, where $V$ denotes the compartment volume. Finally, we denote the initial number of molecules and the corresponding concentration in the $i$-th inlet compartment as $N_{in,i}^{A,init}$ and $c_{in,i}^{A,init}$, respectively. Similarly, we indicate the final number of molecules and the corresponding concentration in the $j$-th outlet compartment by $N_{out,j}^{B,fin}$ and $c_{out,j}^{B,fin}$, respectively.

C. Working Principle

For the description of the working principle we consider Fig. 1 and assume that the initial concentrations in the compartments are zero except for the inlet compartments. The concentrations in the inlets represent the input vector of the matrix multiplication and the output is stored in the concentrations in the outlet compartments as time approaches infinity. We assume that the diffusive processes within the structure are very fast. Thus, once the computation starts, the initial concentrations in the inlets will spread to the connected intermediates by Brownian motion. Thus, after a very short time each inlet and its connected intermediate compartments have the same concentration. If the reaction in the intermediate compartment is slow compared to the diffusion (cf. Sec. III-C for more details), this also holds in the presence of reactions. The rate at which type B molecules are generated in the intermediate compartments depends on three parameters: 1) concentration of type A molecules; 2) reaction rate $r$; 3) compartment volume $V_{i,j}$. Since the first two parameters are the same for two intermediates connected to the same inlet, the number of molecules converted from type A to B only

\[\text{Fig. 1. System architecture of a } 2 \times 2 \text{ matrix multiplication. Inlet, intermediate, and outlet compartments are shown at the top, middle, and bottom.}\]
depends on the volume, i.e., larger volumes lead to more generated type B molecules. Thus, we can use the ratio of the volumes to set the coefficients of the matrix. Finally, as time progresses all B molecules propagate towards the outlet and remain there, since they cannot return. The final B molecule concentration in the outlet compartments is related to the initial inlet concentration via the volumes of the structure.

\[ \text{D. Stochastic Model} \]

Based on the discussion above, we start the derivation of the stochastic model once the inlets and their connected intermediates have the same concentration. Assuming that the reaction in the intermediate compartments can be approximated as first order reaction (cf. (1)), the temporal evolution of the type B molecule concentration can be approximated as first order reaction (cf. (1)), the temporal evolution of the type B molecule concentration can be expressed as

\[ \frac{dN_{B}^{A}(t)}{dt} = rF_{i,j}^{A}(t), \]

with the reaction rate \( r \). The number of B molecules in the intermediate compartments reads as

\[ \frac{dN_{B}^{A}(t)}{dt} = V_{i,j}rF_{i,j}^{A}(t), \]

with \( N_{B}^{A}(t) = c_{B}^{A}(t)V_{i,j} \). Since all intermediates connected to the same inlet have the same concentration it follows that \( c_{B}^{A}(t) = c_{B1}^{A}(t) \) and \( c_{B2}^{A}(t) = c_{B2}^{A}(t) \). Since we assume that diffusion is much faster than the reactions, for each A molecule that reacts another molecule is instantly coming from the inlet. On the other hand, each B molecule that is generated in the intermediate, is instantly transported to the respective outlet. Considering the first inlet (for simplicity we omit the inlet number in the index) this can be written as

\[ F_{\text{in} \to 1}^{A} = F_{\text{in} \to 1}^{B} = rV_{1}c_{B1}^{A} \]

and

\[ F_{\text{in} \to 2}^{A} = F_{\text{in} \to 2}^{B} = rV_{2}c_{B2}^{A}, \]

where \( F \) denotes the flux, the index indicates the flux direction (e.g., \( \text{in} \to (1,1) \)) is the flux from the inlet to intermediate (1,1)) and the superscript denotes the involved molecule type. Thus, the ratio of the fluxes can be expressed as

\[ \frac{F_{\text{in} \to 1}^{A}}{F_{\text{in} \to 2}^{A}} = \frac{V_{1}}{V_{2}}. \]

The initial number of type A molecules in the inlet can be described by the fluxes defined in (4) and (5)

\[ N_{\text{in}1}^{A, \text{init}} = \int_{0}^{t} (F_{\text{in} \to 1}^{A} + F_{\text{in} \to 1}^{A}) dt. \]

Substituting \( F_{\text{in} \to 1}^{A} \) from (6) and using the relation \( F_{\text{in} \to 1}^{A} = F_{\text{in} \to 1}^{B} \) from (4) results in

\[ N_{\text{in}1}^{A, \text{init}} = \frac{V_{1} + V_{2}}{V_{1}} \int_{0}^{t} F_{\text{in} \to 1}^{B} dt = \frac{V_{1} + V_{2}}{V_{1}} N_{\text{out}1}^{B, \text{fin}}|_{t=i,1}, \]

where the final number of B molecules in the first outlet created through A molecules in the first inlet (\( i = 1 \)) is indicated as \( N_{\text{out}1}^{B, \text{fin}}|_{t=i,1} \).

Based on this result we can define the probability that an A molecule initially placed in the first inlet compartment ends up as B molecule in the first outlet compartment

\[ \chi_{1,1} = \frac{N_{\text{out}1}^{B, \text{fin}}|_{t=i,1}}{N_{\text{in}1}^{A, \text{init}}} = \frac{V_{1}}{V_{1} + V_{2}}. \]

Since A molecules in the first inlet compartments can only be related to B molecules in the first or second outlet compartment, the probability for the second outlet compartment is given by \( \chi_{1,2} = 1 - \chi_{1,1} \). Thus, the final number of B molecules in the first outlet created by \( N_{\text{in}1}^{A, \text{init}} \) type A molecules in the first inlet, can be modeled by a binomial distribution

\[ N_{\text{out}1}^{B, \text{fin}}|_{t=i,1} \sim B \left( N_{\text{in}1}^{A, \text{init}}, \chi_{1,1} \right), \]

where \( B(n, p) \) denotes the binomial distribution with the parameters \( n \) (number of independent trials) and \( p \) (probability of success). For a large number of trials \( N_{\text{in}1}^{A, \text{init}} \), a binomial distribution can be approximated by a normal distribution

\[ \frac{N_{\text{in}1}^{A, \text{init}} \chi_{1,1} - \mu}{\sqrt{\sigma^{2}}} \approx N(0, 1), \]

where \( \chi_{1,1} \approx N \left( \mu \pm \frac{\sigma}{\sqrt{V}} \right) \).

Consequently, the final concentration in the first outlet compartment can be expressed as

\[ \frac{\mu + \frac{\sigma}{\sqrt{V}}}{V}, \sigma^{2} \]

where \( V \) denotes the outlet volume. Please note that the variance of \( c_{\text{out}1}^{B, \text{fin}} \) is measure for the computational precision. However, in the following we will only consider the expected value. Based on (15), the expected value of the final concentration in the \( j \)-th outlet compartment can be written as

\[ c_{\text{out}j}^{B, \text{fin}} = \frac{1}{V} \sum_{i=1}^{2} \mu_{i,j} = \frac{1}{V} \sum_{i=1}^{2} V_{i}c_{\text{in}i}^{A, \text{init}} \chi_{i,j}. \]

The relation above can also be written in matrix form, which results in a \( 2 \times 2 \) matrix multiplication

\[ \begin{bmatrix} c_{\text{out}1}^{B, \text{fin}} & c_{\text{out}2}^{B, \text{fin}} \\ c_{\text{out}1}^{A, \text{init}} & c_{\text{out}2}^{A, \text{init}} \end{bmatrix} = \begin{bmatrix} V_{1}+V_{2} \end{bmatrix} \begin{bmatrix} V_{1}+V_{2} \\ V_{1}+V_{2} \end{bmatrix} \begin{bmatrix} V_{1}+V_{2} \end{bmatrix} \begin{bmatrix} V_{1}+V_{2} \end{bmatrix} \begin{bmatrix} N_{\text{in}1}^{A, \text{init}} \\ N_{\text{in}2}^{A, \text{init}} \end{bmatrix}. \]
It is important to note that the first and second columns of the matrix $M$ depends only on the volumes on the left and right hand side of the architecture in Fig. 1, respectively.

E. Volume Selection

To realize a matrix multiplication with arbitrary (positive) matrix coefficients $a, b, c, d$, the following conditions must hold

$$
\begin{bmatrix}
a & b \\
c & d 
\end{bmatrix} = \begin{bmatrix}
\frac{V_{2,1}V_{in,1}}{(V_{1,1}+V_{2,1})^2} & \frac{V_{2,1}V_{in,2}}{(V_{2,1}+V_{2,2})^2} \\
\frac{V_{1,1}V_{in,1}}{(V_{1,1}+V_{2,1})^2} & \frac{V_{1,2}V_{in,2}}{(V_{2,1}+V_{2,2})^2}
\end{bmatrix} = M. \quad (18)
$$

It can be shown that for given matrix coefficients, the volumes could be set as follows to fulfill the condition above: $V_{in,1} = a + c, V_{in,2} = b + d, V_{1,1} = a, V_{1,2} = c, V_{2,1} = b, V_{2,2} = d$ and $V = 1$

$$
\begin{bmatrix}
a & b \\
c & d 
\end{bmatrix} = \begin{bmatrix}
\frac{a(a+c)}{(a+c)} & \frac{b(b+d)}{(b+d)} \\
\frac{c(a+c)}{(a+c)} & \frac{d(b+d)}{(b+d)}
\end{bmatrix}. \quad (19)
$$

However, please note that infinitely many solutions how to choose the volumes to obtain the same matrix $M$ exits. For example, the volumes of the inlet and intermediate compartments can be scaled by the same arbitrary number.

III. Modeling the System Dynamics

In the previous section, we derived a basic model which relates the initial concentration in the inlet to the final concentration in the outlet. In the following, we derive a dynamic system model, which allows to study the temporal evolution of the system states, and, thus, gives more insights into the system behavior.

A. Preliminaries

Reaction-diffusion systems can be described by partial differential equations, which typically cannot be solved analytically for complex geometries. Since we consider a compartment model and assume a uniform concentration within the compartments (see Appendix B), the number of molecules per unit time (flux $F$) that flow through a channel (length $L$, cross-section $S$) between two compartments as follows [9]

$$
dN(t) = F(t) = \frac{DS}{L} (c_2(t) - c_1(t)), \quad (20)
$$

where $c_1(t)$ and $c_2(t)$ correspond to the concentration of compartment 1 and 2 and $D$ denotes the diffusion coefficient. The effect of this molecule flow on the concentrations in the compartments depends on the compartment volume and can be written as

$$
\frac{dc_1(t)}{dt} = \frac{DS}{LV_1} (c_2(t) - c_1(t)), \quad (21)
$$

and

$$
\frac{dc_2(t)}{dt} = \frac{DS}{LV_2} (c_1(t) - c_2(t)), \quad (22)
$$

where $V_1$ and $V_2$ is the volume of compartment 1 and 2, respectively. Please note that for multiple connected compartments the individual molecule flows must be added up. Reactions in a compartment can be incorporated by subtracting a flux of molecules, that are converted from type A to B. Considering a system with two compartments and assuming a reaction with rate $r$ in compartment one, the concentration in this compartment can be defined by slightly modifying (21)

$$
\frac{dc_1(t)}{dt} = \frac{DS}{LV_1} (c_2(t) - c_1(t)) - rc_1(t), \quad (23)
$$

and the concentration in compartment two does not change (cf. (22)). An unidirectional transport between two compartments can be modeled by omitting the destination concentration. For example, for an unidirectional flow from the first to the second compartment only the expression $c_2(t)$ on the right hand side of (21) and (22) need to be removed.

B. Dynamic Model

We now use the results from the previous section to model the dynamic behavior of the system. We use $I = 2$ and $J = 2$ to represent the number of inlets and outlets, respectively (see Fig. 1).

1) Inlet Compartment: The concentration of type A molecules in the $i$-th inlet can be described as follows

$$
\frac{dc_{in,i}(t)}{dt} = \frac{1}{V_{in,i}} \left( -J \frac{DS}{L} c_{in,i}(t) + \sum_{j=1}^{J} \frac{DS}{L} c_{in,j}(t) \right) \quad (24)
$$

2) Intermediate Compartments: The concentration of type A molecules in the intermediate compartments is given by

$$
\frac{dc_{i,j}(t)}{dt} = \frac{1}{V_{i,j}} \left( - \left( rV_{i,j} + \frac{DS}{L} \right) c_{i,j}(t) + \frac{DS}{L} c_{in,i}(t) \right) \quad (25)
$$

Moreover, the concentration of type B molecules can be expressed as

$$
\frac{dc_{i,j}^B(t)}{dt} = \frac{1}{V_{i,j}} \left( rV_{i,j} c_{i,j}(t) - \frac{DS}{L} c_{i,j}^B(t) \right) \quad (26)
$$

3) Outlet Compartment: The concentration of type B molecules in the $j$-th inlet can be described as follows

$$
\frac{dc_{out,j}(t)}{dt} = \frac{1}{V} \left( \sum_{i=1}^{I} \frac{DS}{L} c_{i,j}(t) \right) \quad (27)
$$

4) Overall Model: Since the above system consists of linear equations it can be formulated in matrix-vector notation

$$
\frac{dc(t)}{dt} = Tc(t), \quad (28)
$$

where the vector $c$ includes all compartment concentrations and the respective factors (e.g., $DS/L$) are collected in the matrix $T$. It can be solved numerically and analytically for given initial conditions. However, the analytical expressions are very bulky and, thus, are not shown due to space constraints. Moreover, by applying frequency analysis and the final value theorem of the Laplace transformation we obtain for the ideal case (i.e., $r \to 0$)

$$
e^{fin} = \lim_{r \to 0, s \to 0} s \frac{1}{sI - T} c(t = 0), \quad (29)
$$
where $I$ denotes the identity matrix and the final concentrations in all compartments are included in the vector $c^{\text{fin}}$. Thus, the concentrations in the outlet compartments included in $c^{\text{fin}}$ corresponds to the result $c^{\text{fin}}_{\text{out}}$ given in (17). Please note that the dynamic model also allows to determine the behavior of the non-ideal systems (i.e., $r > 0$) and to estimate the time until the matrix multiplication is finished, i.e., when the final concentrations are achieved.

C. Required Conditions

In this section, we formalize the two assumptions that have been made throughout the work. The first assumption deals with the fact that the reaction is much slower than the diffusive processes, which can be ensured if the following condition holds (see Appendix A for more details)

$$DS \gg Lr \max(V_{i,j}),$$

where $\max(V_{i,j})$ denote the largest volume of the connected intermediate compartments. The second assumption deals with the uniform concentrations within the compartments. For this case the required condition is given by (see Appendix B for more details)

$$\frac{d^2}{2} \ll \frac{L}{S c_{\text{max}}},$$

where $d$ indicates the largest distance between two points in a compartment (e.g., in a spherical compartment $d$ corresponds to the diameter), and $c_{\text{max}}$ denotes highest allowed inlet concentration. For typical $r$ and $D$, the two conditions above hold in the micro and nano-scale.

IV. Simulation Results

In this section, we validate the proposed matrix multiplication given in (17) and the dynamic model presented in Sec. III through results obtained from particle based simulations (PBSs). For the PBS we used the AccoRD simulator presented in [10]. The parameters for the numerical evaluation are summarized in Tabs. I and II and were chosen taking into account the conditions derived in Sec. III-C. For the following study, we chose two different initial inlet concentrations given by the vectors $c^{(1),\text{init}}_{\text{in}} = [1 \ 2]^T \times 10^{21}$ molecules/m$^3$ and $c^{(2),\text{init}}_{\text{in}} = [2 \ 1]^T \times 10^{21}$ molecules/m$^3$ and the matrix

$$M = \begin{bmatrix} 1 & 2 \\ 3 & 4 \end{bmatrix}.$$ (32)

Thus, the matrix multiplication of the two input vectors leads to the following concentration in the outlets given by the vectors $c^{(1),\text{fin}}_{\text{out}} = [5 \ 11]^T \times 10^{21}$ molecules/m$^3$ and $c^{(2),\text{fin}}_{\text{out}} = [4 \ 10]^T \times 10^{21}$ molecules/m$^3$.

Figs. 2 and 3 show the concentration of type B molecules in the outlet compartments. We observe that the results from the dynamic model and the results from PBS match very well and both converge to a steady state (indicated by the black lines). This steady state corresponds to the final concentration given by the vectors $c^{(1),\text{fin}}_{\text{out}}$ and $c^{(2),\text{fin}}_{\text{out}}$, which validates the matrix multiplication given in (17).

V. Conclusions

In this paper, we proposed a novel reaction-diffusion-based nano-machine architecture that performs matrix multiplications, which is a basic operation for machine learning algorithms. We presented a stochastic and dynamic model of the system and derived necessary conditions that must be satisfied for the structure to work. These condition are especially
fulfilled in the nano-scale. By PBS we confirmed the derived models and the validity of the proposed architecture to perform matrix multiplications. This work is a first step towards the development for nano-scale computing architectures especially suited for ML algorithms. Interesting topics for future work include the extension of the proposed architecture to arbitrary matrix dimensions and negative coefficients and its application to neural networks.

REFERENCES


APPENDIX A

ASSUMPTION 1: RELATION BETWEEN REACTION AND DIFFUSION

To derive a sufficient condition for the diffusion to be much faster than chemical reactions, we utilize the principle of time-scale separation [11]. For this purpose, we assume that the volumes of the inlets are much larger than those of the connected intermediates. Thus, it can be deduced from (24) and (25) that the change in the concentration of \( A \) molecules is much faster in the intermediate compartments than in the inlets. Therefore, we can assume that the concentration of \( A \) molecules in the intermediates exhibits a quasi-steady state, which can be calculated by setting the left hand side of (25) to zero. W.l.o.g we consider only inlet \( i = 1 \) in the following. We obtain \( \frac{dA}{dt} = \frac{G_{1,1}c_{A}}{V_{1,1}} \) and \( \frac{dA}{dt} = \frac{G_{1,2}c_{A}}{V_{1,2}} \) with \( G_{i,j} = \frac{DS}{V_{i,j}r_{L}+DS} \). The generation rate of \( B \) molecules in the intermediates is given by (2) and, thus, the ratio of \( B \) molecules in the intermediate compartments connected to the first inlet can be expressed as

\[
\frac{dN_{B,1}}{dN_{B,1}} = \frac{rV_{1,1}G_{1,1}c_{A}}{rV_{1,2}G_{1,2}c_{A}} = \frac{V_{1,1}G_{1,1}}{V_{1,2}G_{1,2}}.
\]

This ratio differs from the ratio derived from (3), which corresponds to the case of \( r \to 0 \), by the factor

\[
\frac{G_{1,1}}{G_{1,2}} = \frac{rV_{1,2}L + DS}{rV_{1,1}L + DS}.
\]

Actually, this factor is a measure for the computational error when the reactions are not infinitely slow (\( r \to 0 \)), which is small for \( LR_{i,j} \ll DS \). Thus, the condition that ensures that the reaction is much slower than the diffusive processes can be stated as

\[
DS \gg LR_{m}(V_{i,j}),
\]

where \( LR_{m}(V_{i,j}) \) denote the largest volume of the connected intermediate compartment. Note, that the left hand side of this equation scales approximately with the second order of the diameter of a compartment, while the right hand side scales approximately with the fourth order. Thus, the smaller the overall structure, the easier it becomes to fulfill the condition.

APPENDIX B

ASSUMPTION 2: UNIFORM CONCENTRATION

All models derived in this work are based on the assumption that the concentration in the compartments is uniform. In the following, we derive a condition to ensure this assumption. The time it takes for a molecule to propagate a distance \( d \) within the compartment according to Brownian motion is given by [9]

\[
\tau_{1} = \frac{d^{2}}{2D},
\]

where \( D \) denotes the diffusion coefficient. If we chose \( d \) as the largest distance between two points in a compartment, we can interpret this time as a measure for how long it takes until the system has forgotten the initial position of the molecule. Moreover, the maximum rate at which molecules propagate between two compartments can be computed based on (20) and reads as follows

\[
\max \left( \frac{dN}{dt} \right) = \frac{DS_{\text{max}}}{L},
\]

where \( c_{\text{max}} \) denotes highest possible inlet concentration and \( L \) and \( S \) are the length and cross-section of the channel between two compartments, respectively. Consequently, the shortest time interval in which consecutive molecules arrive is given by

\[
\tau_{2} = \frac{L}{DS_{\text{max}}}
\]

The concentration in a compartment can be considered as uniform, if no molecule accumulation occurs or in other words, when a molecule arrives at the compartment the system should have forgotten about the previously arrived molecule. This is fulfilled if \( \tau_{1} \ll \tau_{2} \) holds and, thus, the uniform concentration in a compartment can be ensured by the following condition

\[
\frac{d^{2}}{2} \ll \frac{L}{S_{\text{max}}}.
\]