Investigation of Different Chemical Realizations for Molecular Matrix Multiplications

Stefan Angerbauer\textsuperscript{1}, Nunzio Tuccitto\textsuperscript{2}, Giuseppe Trusso Sfrazetto\textsuperscript{2}, Rossella Santonocito\textsuperscript{2}, and Werner Haselmayr\textsuperscript{1}

\textsuperscript{1}Institute for Communications Engineering and RF-Systems, Johannes Kepler University Linz
\textsuperscript{2}Dipartimento di Scienze Chimiche, Universita’ di Catania

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Abstract

Intelligent nano-machines are a promising candidate technology for the next generation of health care. The realization of such units relies on novel, unconventional approaches, to allow for bio-compatibility and managing space constraints. In this work, we present three chemical processes, that can be used to realize a recently proposed molecular matrix multiplication unit on the lab-scale. The matrix multiplication is the fundamental operation for the realization of neural networks and, therefore, artificial intelligence. Hence, this work presents an important step towards practical realization of intelligent nano-machines for the next generation health care.
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Stefan Angerbauer¹, Nunzio Tuccitto², Giuseppe Trusso Sfrazetto², Rossella Santonocito², and Werner Haselmayr¹

¹Institute for Communications Engineering and RF-Systems, Johannes Kepler University Linz, Austria
²Dipartimento di Scienze Chimiche, Università di Catania, Italy

Abstract—Intelligent nano-machines are a promising candidate technology for the next generation of health care. The realization of such units relies on novel, unconventional approaches, to allow for bio-compatibility and managing space constraints. In this work, we present three chemical processes, that can be used to realize a recently proposed molecular matrix multiplication unit on the lab-scale. The matrix multiplication is the fundamental operation for the realization of neural networks and, therefore, artificial intelligence. Hence, this work presents an important step towards practical realization of intelligent nano-machines for the next generation health care.

Index Terms—Internet of Bio-Nano Things, Machine Learning, Molecular Communications, Unconventional Computing

I. INTRODUCTION

The past century has been dominated by rapid developments in semiconductor technology leading to the broad accessibility of custom electronic computing units, reaching from microcontrollers over field-programmable gate arrays (FPGA) to personal computers (PCs). The majority of these devices employ digital logic to carry out computational task, which is a highly robust and reliable technology, that has been optimized for decades. However, as research on computing progresses, a number of drawbacks of the technology arise [1], with high power consumption and worse parallelism capabilities compared to analog computing being the most significant ones in terms of classical computer science. Furthermore, there are classes of problems or specific scenarios, where other computing concepts, referred to as ”unconventional computing” might exhibit superior performance. Typical examples of such unconventional computing concepts are quantum computing [2] and molecular computing [3]. While quantum computing has clear advantages in terms of computation speed and the ability to solve complex problems, molecular computing provides a high degree of biological compatibility and the ability to use chemical processes as alternative energy sources. Hence, the latter is a promising approach for the realization of in-body computing units for biomedical applications, especially as nano-machines (NMs) in the Internet of Bio-Nano Things (IoBNT) [4]. A NMs is a tiny devices placed in the human body to carry out tasks like sensing, processing and transmitting molecular information. The IoBNT is a heterogeneous network of multiple NMs that is connected to the Internet. It enables the next level of personalized health monitoring and care. To make this visionary concept reality, communication and computing in the molecular domain is required. Although many works on molecular communication exists [5], the contributions in molecular computing are limited. For example, in [6], chemical logic gates were introduced, which could serve as the basis for chemical computers. However, in the light of the space constraint in the nano-domain, other authors proposed analog molecular computing devices, which were specifically designed for a given task; mainly for the realization of molecular neural networks [7], [8]. These works where supported by experiments using living biological entities. In a recent work [9], a novel matrix multiplication unit was introduced. It is based on diffusion-based propagation between non-living compartments and chemical reactions within some compartments. Although, the potential of the proposed concept was shown through comprehensive theoretical and simulative studies, there is no experimental verification yet. Thus, the aim of this work is to fill this gap. In particular, we present a first chemical realization on the lab-scale, which is an important step towards a micro/nano-scale implementation.

The organization of the paper is as follows: In Sec. II, we revisit the theoretical concept of the matrix multiplication and present adaptions required for the the lab-scale implementation. In Sec. III, we introduce three chemical lab-scale realizations and analyze the experimental results in Sec. IV. Finally, Sec. V provides concluding remarks and an outlook on the implementation in the micro/nano-domain.

II. THEORETICAL CONCEPT AND PRACTICAL ADAPTATIONS

The theoretical framework of a positive valued $2 \times 2$ matrix multiplication structure was introduced in [9] and the generalization to arbitrary matrices and neural networks was carried out in two follow-up works [10] and [11]. In this work, we propose the lab-scale realization of a positive valued $2 \times 2$ matrix multiplication, which also builds the basis for more advanced structures. The following subsections briefly summarize the proposed computation concept presented in [9] and present the required adaptions for the lab-scale implementation¹.

¹Please note, that system was designed specifically for application on the micro/nano-domain and, thus, some of the proposed mechanisms are not available on the lab-scale. For this reason, they will be replaced by suitable alternatives.
A. Computation through Substance Transport and Reaction

1) Theoretical Concept: The proposed theoretical structure is depicted in Fig. 1. Circles indicate compartments (from top to bottom inlet, intermediates and outlets), connecting lines indicate channels and arrows indicate substance transport direction. The involved substances (input molecule A, reaction partner C and output molecule B) are written in sans-serif. On the micro/nano-scale, this concept works as follows: The input vector is encoded in the A concentration in the two inlet. Since the structure is very small, diffusion can be considered to be fast. The molecules placed in one inlet diffuse almost immediately to the intermediates and, hence, one input and all its intermediates have the same concentration. If the reaction in the intermediates is sufficiently slow it will not influence this concentration equilibrium significantly and we can assume, that this condition also holds in the presence of the reaction. Since the intermediates have different volumes, but the same concentration, the reaction A(+)C → B taking place within them will produce different amounts of B molecules, where larger volumes produce more molecules than smaller ones. Eventually, all molecules within an inlet have been converted in one of the connected intermediates. The fraction of A molecules placed in inlet i and traveling to outlet j via conversion in intermediate (i,j) can be written as [9]

$$\chi_{i,j} = \frac{V_{i,j}}{\sum_{j=1}^{I} V_{i,j}},$$  \hspace{1cm} (1)

which obviously cannot become larger than one. To allow for an arbitrary positive amplification from inlet to outlet, we introduce the ratio

$$G_{i,j} = \frac{V_{i,j}}{V_{i}}.$$  \hspace{1cm} (2)

The implication of this gain factor is, that if the outlet volume is smaller than the inlet volume, the same number of molecules placed within it will lead to a larger concentration since the concentration is defined as the number of molecules per volume. The relationship between inlet and outlet concentration can be written as [9]

$$C_{\text{out},j}^{B,\text{fin}} = \sum_{i=1}^{I} \chi_{i,j} G_{i,j} C_{\text{in},i}^{A,\text{init}}.$$  \hspace{1cm} (3)

Thereby, $C_{\text{out},j}^{B,\text{fin}}$ indicates the final concentration of B molecules in the jth outlet and $C_{\text{in},i}^{A,\text{init}}$ the initial concentration of A molecules in the ith inlet. It is important to note that (3) corresponds to the matrix multiplication $C_{\text{out}} = MC_{\text{in}}$, with $C_{\text{in}}$ and $C_{\text{out}}$ vectors containing the I initial input concentrations and J final outlet concentrations and M a $I \times I$ matrix.

2) Practical Realization: The concept presented above can be translated to the lab-scale with some minor adjustments. These adjustments are mainly linked to the transport of substances. As introduced above, the factor $\chi_{i,j}$ indicates the fraction of molecules from the inlet i ending up in outlet j. This substance transport is achieved by a combination of reaction and diffusion on the micro/nano-scale. On the much larger lab-scale, however, diffusion is a very slow process. Therefore, we replace the reaction-diffusion driven transport by a manual transport, i.e., a pipette is used to transfer 100\% of the substance placed in inlet i either to intermediate (i,j) or directly outlet j, depending on the chosen procedure. The gain $G_{i,j}$ is realized in the exact same manner as on the micro/nano-scale, i.e., by the ratio between inlet and outlet volume. It is important to point out, that (3) only contains fractions of volumes and never absolute values of volumes. Hence, with the aforementioned adaption to realize $\chi_{i,j}$, we gain independence of the actual amounts of substances used, i.e., carrying out the same experiments, while doubling all involved volumes will yield the same outcome.

B. Measurement in Experiments

The theoretical concept uses molecular concentrations as input and output of the computation. In the experimental realization, we need to include an additional step, that is measuring the input and output concentration, to verify, that the structure indeed performs the desired task. We use two methods to determine the input and output concentration.

1) Weight: Using an electronic scale, we measure the weight of the substances injected into the inlet and obtained in the outlet. This approach eliminates the factor $G_{i,j}$, since we indirectly measure the number of molecules instead of the concentration.

2) Spectroscopy: Ultraviolet-visible (UV-Vis) spectroscopy is a technique that analyzes the absorption of ultraviolet-visible light by molecules to determine their concentration in a sample. In order to use this technique, the absorbance spectrum of the used molecules (A and B) needs to be known in advance. The particular challenge using this technique is,
that it works only reliably for concentration below a specific threshold. Hence, when using this approach, we choose the transferred volumes and initial concentrations such, that we stay within the valid range. This can be easily achieved, by selecting the input concentrations accordingly.

III. PROPOSED CHEMICAL REALIZATION

In the following, we propose three methods for a chemical realization of the theoretical matrix multiplication concept on the lab-scale. We chose the matrix

\[
M = \frac{1}{4} \begin{bmatrix} 1 & 2 \\ 3 & 4 \end{bmatrix},
\]

and for each method a different input vector is used, to demonstrate the general validity of the proposed approach.

A. Method 1: Phase-Transition Reaction

The overall experimental procedure is depicted in Fig. 2. We used BODIPY-based dye and synthesized it according to the procedure given in [12]. The corresponding UV-Vis spectrum is shown in Fig. 3. This substance is soluble in both chloroform and water, but has much higher affinity for chloroform. Its concentration can be measured in both substances by UV-Vis spectroscopy. If the substance is dissolved in water, we call it \(A\) and if it is dissolved in chloroform, we call it \(B\). We add different amounts (indicated by different colors in Fig. 2) of the dye to water to encode the two inlet concentrations. The amount of transferred solution is indicated by the numbers in the figure. The inlet volume is the sum of substances transported away from it, for example, inlet 1 contains 8 units of volume, of which 2 are transferred to outlet 1 and 6 are transferred to outlet 2. To obtain the molecule \(B\) (i.e., dye in chloroform), we shake the outlets, which leads to a transition of the dye from water to chloroform. Hence, after this step, the chloroform is colored and the water is colorless. Then we remove the water and evaporate the chloroform until it is reduced to eight units. The flask with the reduced chloroform is considered as the output and the concentration can be measured by UV-Vis spectroscopy. Next, we show that the proposed procedure realizes the intended matrix: The gains are \(G_1 = \frac{V_{in,1}}{8} = \frac{5}{8} = 1\) and \(G_2 = \frac{V_{in,2}}{8} = \frac{12}{8} = \frac{3}{2}\) and the transfer fractions are \(\chi_{1,1} = \frac{V_{1,1}}{V_{1,1} + V_{1,2}} = \frac{2}{5}, \chi_{1,2} = \frac{6}{8}, \chi_{2,1} = \frac{4}{12}\). Hence, according to (3) the output concentrations can be computed by

\[
C_{B, fin, out, 1} = \frac{1}{4} C_{in, 1} + \frac{2}{4} C_{in, 2},
\]

\[
C_{B, fin, out, 2} = \frac{3}{4} C_{in, 1} + \frac{4}{4} C_{in, 2},
\]

which realizes the desired matrix given in (4). This justification is true for any inlet concentration, which is why the same procedure can be used for arbitrary concentrations.

It is important to note that the same calculations can be carried out for the following methods and, thus, are omitted for the sake of compactness.

B. Method 2: Precipitation Reaction

In this method, we incorporate a chemical reaction that involves a transformation of substances. We choose the reaction

\[
S^{2-} + Cu^{2+} \rightarrow CuS \downarrow,
\]

and define \(A := S^{2-}\), \(C := Cu^{2+}\) and \(B := CuS\). The reaction takes place in water, in which \(A\) is dissolved and \(C\) is added to trigger the reaction. The downward pointing arrow in (7) indicates, that the solid \(B\) will precipitate to the bottom of the glass. Hence, this reaction can be viewed as a

\[
\text{In fact, a small amount of dye remains in the water. This is the reason, why we prefer to choose large amounts of chloroform to increase the transfer efficiency.}
\]
type of unidirectional transport, like the one connecting the intermediates of Fig. 1 to the outlets. A visual representation of Method 2 is depicted in Fig. 4. Again, we realize the matrix (4) and for this experiment we choose the input vector $C_{in} = [0.66 \ 1.32] \text{mol L}^{-1}$. The transport is realized in the same way as described for Method 1. Then, C molecules are separated by filtering and the amount of substance ending up in each outlet is weighted. Hence, the output of this method is actually a weight, which is then converted to a molarity by first converting to mol and then dividing by the volume.

C. Method 3: Acid to Base Reaction

Method 3 uses the pH colorimeter indicator phenolphthalein as molecule A and B. This molecule is colorless in an acidic environment and pink in a basic environment. The inlets contained HCl 0.1M-solution (i.e., $0.1 \text{mol L}^{-1}$) with different amounts of A added to encode the initial concentration $C_{in} = [50 \ 5] \times 10^{-6} \text{mol L}^{-1}$. Then, the same procedure as in Method 1 was carried out, where no chloroform was used, and instead of shaking, 1M NaOH was added dropwise, to change the pH from acidic to basic. The outlet concentration was again measured by a UV-Vis spectrometer.

IV. Analysis

In the following, we present and analyse the outcomes of the experiments for the methods 1, 2 and 3. Therefore, each experiment was carried out 10 times and input and output concentrations/weights were recorded. The expected value was calculated using the respective input vectors (described in the previous section for each of the individual methods) and the exact matrix given in (4). We use two types of metrics:

• **Normalized Ratio of Outlet Concentrations**: This metric is based on the ratio between the two outlet concentrations for each method (normalized by the expected ratio). It ignores a constant attenuation, as long as it affects all matrix weights equally. This can be modeled by replacing $G_{i,j}$ in (3) by a term $G_{i,j} = G_0 G_{i,j}$, where $0 < G_0 < 1$ is a constant attenuation factor, which cancels out if the ratio of two outlets is considered.

• **Normalized Outlet Concentrations**: For this metric, we normalize each outlet for each method by its expected value. The mean of this value is influenced by the aforementioned factor $G_0$, i.e., if there is attenuation this metric will yield a mean-value smaller than one. On the other hand the standard deviation of this metric is a measure for the computational uncertainty.

Please note, that it is easily possible to correct a wrong gain (e.g., by using more of substance A or further reducing V), while a mismatch in this metric indicates a methodical error, which cannot be easily corrected.

A. Ratio of Outlet Concentrations

We define the outlet concentration ratios by

$$r_k = \frac{C_{out,1,k}}{C_{out,2,k}},$$

and

$$\hat{r} = \frac{C_{out,1}}{C_{out,2}},$$

where the index $k$ indicates samples from the experiment (i.e., $k \in \{1, 2, 3 \ldots 10\}$) and the absence of an index indicates the theoretical value. Fig. 5 shows the plot of the metric $r_k = r_k/\hat{r}$ and the corresponding box-plot. We notice, that all three methods give a median value close to one, with method 1 being the closest and method 2 being the furthest away from the expected value. However, the deviation of method 2, is due to an outlier in the data. From a visual examination of the plots, we see, that the uncertainty of this metric rarely exceeds 10%.
G system, e.g., by multiplying the outlet volume by a factor by incorporating the respective factor into the design of the as already mentioned, we can easily correct this imperfection chloroform, which is due to thermodynamic reasons. However, A is the incomplete transition of be compensated. In the case of method 1, this mechanism G respective medians for method 1 are around be realized exactly the intended operation. The methods indeed realize exactly the intended operation. The visualization of the normalized outlet concentrations for each method in the micro/nano-domain, which is an important step towards its application in the IoBNT.

B. Normalized Outlet Concentrations

We define the normalized outlet concentration by

\[ n_{l,k} = \frac{C_{\text{out},l,k}}{\mu_{\text{out},l}} \]  

(10)

where each of the \( k \) samples for the \( l \in \{1, 2\} \) outlets is normalized by the expected value of that outlet. This procedure is carried out for each method and the corresponding plot is shown in Fig. 6. We notice, that this metric gives medians close to one for the methods 2 and 3, indicating, that these methods indeed realize exactly the intended operation. The respective medians for method 1 are around \( G_0 = 0.6 \), which indicates an additional attenuation mechanism that needs to be compensated. In the case of method 1, this mechanism is the incomplete transition of A molecules from water to chloroform, which is due to thermodynamic reasons. However, as already mentioned, we can easily correct this imperfection by incorporating the respective factor into the design of the system, e.g., by multiplying the outlet volume by a factor \( G_0 = 0.6 \) (this can be seen substituting the definition of \( G_{l,j} \) from the previous subsection into (3) and then multiplying \( V \) by \( G_0 \)). Finally, we compute mean \( \mu \), standard deviation \( \sigma \) and ratio \( R = \sigma / \mu \) for each method and each output. The results are summarized in Tab. I. We notice, that the uncertainty of each output, reflected by \( R \) is in the same order of magnitude for all methods. Hence, all methods are potential candidates for future realizations of the proposed concept. Yet, in future works, we will identify and mitigate causes of the current computational uncertainty.

V. CONCLUSION AND OUTLOOK

In this work, we presented three methods for the chemical realization of a recently proposed molecular matrix multiplication unit on the lab-scale. The analysis revealed that all three methods provide a reasonable accuracy. Based on the proposed lab-scale implementation, future work include the realization in the micro/nano-domain, which is an important step towards its application in the IoBNT.

### Table I

<table>
<thead>
<tr>
<th>Method</th>
<th>Outlet 1</th>
<th>Outlet 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>( \mu = 0.6292 )</td>
<td>( \mu = 0.6250 )</td>
</tr>
<tr>
<td></td>
<td>( \sigma = 0.0772 )</td>
<td>( \sigma = 0.0306 )</td>
</tr>
<tr>
<td></td>
<td>( R = 0.1226 )</td>
<td>( R = 0.0489 )</td>
</tr>
<tr>
<td>M2</td>
<td>( \mu = 0.9092 )</td>
<td>( \mu = 1.0220 )</td>
</tr>
<tr>
<td></td>
<td>( \sigma = 0.0445 )</td>
<td>( \sigma = 0.1546 )</td>
</tr>
<tr>
<td></td>
<td>( R = 0.0460 )</td>
<td>( R = 0.1513 )</td>
</tr>
<tr>
<td>M3</td>
<td>( \mu = 1.0000 )</td>
<td>( \mu = 0.9867 )</td>
</tr>
<tr>
<td></td>
<td>( \sigma = 0.1333 )</td>
<td>( \sigma = 0.1242 )</td>
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<tr>
<td></td>
<td>( R = 0.1333 )</td>
<td>( R = 0.1259 )</td>
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### References


