Fluidic Molecular Processing and Interfacing Devices

Marina Alexandra Lyshevski[*] and Sergey Edward Lyshevski[**]

[*]Microsystems and Nanotechnologies, Webster, NY 14580-4400, USA
[**]Department of Electrical Engineering, Rochester Institute of Technology, Rochester, NY 14623, USA
E-mail: E.Lyshevski@rit.edu and Sergey.Lyshevski@mail.rit.edu

ABSTRACT

We study *fluidic* processing devices and interfacing modules to perform data processing, interfacing and other related tasks utilizing molecular electrochemomechanical transitions and interactions. We consider various *fluidic* devices as *modular* primitives in order to: (i) Develop and examine alternative processing paradigms typifying *natural* processing platforms; (ii) Interface microapparatuses with biomolecular and *natural* systems establishing a sound micro-bio interface. Data processing and memory storage by *fluidic* devices cannot be equated to information processing exhibited by living systems. However, the proposed solution contributes to the *natural* and molecular data processing, memories, communication and interfacing. The *fluidic* devices are examined studying the synthesis issues, electrochemomechanical transitions, control of *microscopic* particles, etc. The device physics, expected performance and functionality are reported and discussed.

Keywords: biomolecule, *fluidic*, interfacing, processing

1. INTRODUCTION

The activity of brain neurons has been extensively studied using single microelectrodes as well as microelectrode arrays to probe and attempt to affect the activity of a single neuron or assembly of neurons in brain and neural culture. Unfortunately, these attempts have been only partially successful due to enormous fundamental, experimental and technological problems. For example, a great deal of effort has been applied attempting to integrate neurons and microelectronics with a very modest progress [1, 2]. It is unlikely that the micro-bio interface can be achieved using conventional *solid*-centered microelectronic solutions. This paper contributes to the aforementioned developments by examining alternative solutions in design of interfacing modules.

We also focus on a sound solution in processing by researching computing and memory utilizing molecular electrochemomechanical transitions and interactions. From processing viewpoints, our solution may have a limited practicality due to technological difficulties and existence of outstanding solutions, e.g., microelectronics and integrated circuits (ICs). However, the developments undertaken are very important and contribute to long-standing problems of biophysics. It may be expected that *fluidic* processing devices and interfacing modules may affect or empower biotechnology, science, engineering and medicine by contributing to:

1. Biophysics fundamentals;
2. Basic research in *natural* processing (*natural* computing);
3. Sound technological developments;
4. Interfacing and integration of implantable biocompatible microelectronics, microelectrodes, microsensors and other apparatuses.

These problems are forefronts of science, engineering and technology. We propose a *fluidic* molecular processing device which mimics, to some extent, a neuronal processing-and-memory primitive or a brain neuron. In general, data processing and memory storage can be accomplished by various electrochemomechanically-induced transitions, interactions and events. For example, release, propagation and binding/unbinding of movable molecules result in state transitions to be utilized. Due to unsolved fundamental problems, complexity and technological limits, one may not coherently comprehend, mimic and prototype information processing in living systems. We typify 3D topologies/organizations of biosystems, utilize molecular hardware, and employ molecular transitions. These innovations imply novel synthesis, design, aggregation, utilization, functionalization and other features. We proposed to utilize specific electromechanical transitions (bond formation/braking, electron exchange, electron flow and other) between stationary biomolecules and

- *information*/*routing*/*executing* carriers for processing devices,
- *interfacing* and *routing* carriers in interfacing modules.

Various molecules and ions, utilized in neurons, are examined. Examples are reported.

2. *FLUIDIC* PROCESSING AND INTERFACING DEVICES

Utilizing 3D topology/organization of biomolecular assemblies, observed in *natural* systems, the *engineered fluidic* molecular processing device (^{MP}device) is illustrated in Figure 1. The inner enclosure can be made of proteins, porous silicon or polymers to form membranes with fluidic channels with the binding sites which ensure the functionality and selectivity. The *information*/*routing*/*executing* or *interfacing* carriers are encapsulated in the outer enclosures or cavities. The release and steering of different carriers are controlled by the control apparatus utilizing *passive* and *active* mechanisms. The electrochemo-

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mechanical transitions, caused by the *information* carriers, result in the logic and memory events. Multiple-valued state transitions imply that computing, processing and memory storage can be performed on the high radix. Using *routing* carriers, persistent and robust morphological reconfigurable networking can be achieved. This ensures a reconfigurable networking processing-and-memory organization.

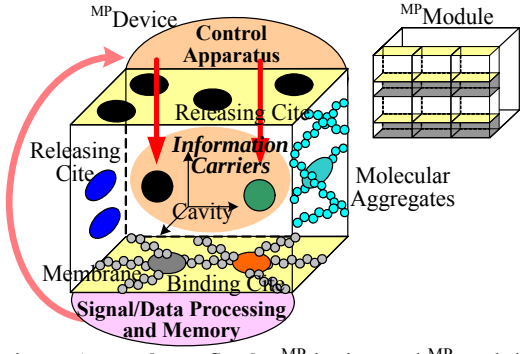

Figure 1. *Synthetic fluidic* MP device and MP module with 3×2×2 devices

The released *routing* carriers are steered in the fluidic cavity to the binding sites resulting in the binding/unbinding of *routers* to the stationary molecules. The binding/unbinding events lead to reconfigurable routing ensuring reconfiguration.

The proposed *fluidic* MP device mimics, to some extent, a neuron with synapses, membrane, channels, cytoplasm, microtubules, organelles, etc. Specific ions, molecules and enzymes propagate in the synaptic cleft and can pass through the membrane channels. In the proposed MP device, the carriers pass the porous membrane and propagate in the cavity. The molecules (*information* and *routing* carriers) bind to the specific receptor sites, while enzymes free molecules from binding sites. Binding and unbinding of molecules result in the electrochemomechanical transitions. The released carriers are controlled by changing the electrostatic potential or thermal gradient. Control of carriers cannot be accomplished through preassigned steady-state conditional logics, synchronization, timing protocols and other conventional concepts.

The motion and dynamics of the carrier release, propagation, binding/unbinding and other events are examined. The goal is to achieve a controlled motion and functionality of *microscopic* carriers. Distinct control mechanisms (electrostatic, electromagnetic, thermal, hydrodynamic, etc.) allow one to uniquely utilize selective control ensuring high performance and enabling functionality. The controlled *active* transport of molecules and ions in the fluidic cavity and channels are examined. Having proposed a hardware solution, the carrier displacement $\mathbf{r}_i$ is controlled by the control vector $\mathbf{u}$. Released carriers propagate in the fluidic cavity. These carriers are controlled by a control apparatus varying $F_n(t,\mathbf{r},\mathbf{u})$ and $V_k(\mathbf{r},\mathbf{u})$ [2]. This apparatus is comprised of molecular assemblies which change the temperature gradient or the electric field intensity. The state transitions occur in the anchored processing polypeptide or organic molecular complexes as *information*/*routing*/*executing* or *interfacing* carriers bind/unbind. For example, conformational *switching*, charge changes, electron transport and other phenomena can be utilized. The transition time of electronic, photoelectric and electrochemomechanical state transitions ranges from psec to μsec. The molecular hardware predefines the phenomena (effects) utilized, as well as device functionality. For example, *electromechanical switching* can be accomplished by biomolecules. It is feasible to design and potentially synthesize aggregated networks of reconfigurable *fluidic* MP devices. These devices and modules are characterized in terms of input-output functionality, activity, performance, etc. To overcome the fabrication deficiencies, one may utilize the cultured neurons as modules.

To relate neurons to the proposed concept, one recalls the so-called *fluid mosaic model* of the biological plasma membrane. In the membrane, most of the lipids and membrane proteins are held together by hydrophobic attractions which are weaker then covalent bonds. The certain biological conditions (temperature, pH, etc.) must be guaranteed. The lipid bilayer is the main fabric of the membrane, while proteins affect the membrane functionality. There are more then 50 different plasma proteins. For example, glycoproteins (proteins with covalently bonded carbohydrates) are important in intracellular recognition. The selective permeability of membrane is defined by the lipid bilayer specificity, as well as by transport proteins and ion channel plasma membrane proteins.

There are two types of transport across the biological membrane depending on the particles being transported, e.g., passive and active. The channel proteins form hydrophilic pores across membrane. They are narrow, highly selective and referred as *ion channels*. The transport efficiency and its rate were extensively studied. It was found that ion channel transport, as compared to transport mediated by carrier proteins, ensures rate ~1000:1. Control of the transport through the ion channel is essential to maintain basic cell functions.

In most cases, receptors are transmembrane proteins on the target-cell surface. When they bind a released extracellular molecule (ligand), receptors become activated and undergo transitions which define cell activity. Receptors also can reside inside the cell, and the ligand has to enter the cell to activate it. Neurons possess various complex processing-related transitions and mechanisms. The functionality depends on the biomolecule-protein recognition, binding, unbinding and other transitions.

The release and suppression of neurotransmitters, and their role on action potential and other transitions were extensively studied in the literature. For example, some results are reported in [3, 4].

3. Energetics Estimates

The energetics of neurotransmitters, biomolecules and *information carriers* is analyzed. In neurons, synaptic

changes proceed through the release of neurotransmitters, activation/deactivation of synaptic receptors, protein conformational changes, etc. The activation of the acetylcholine receptors is the most researched. We estimate the binding energy of the low-molecular-weight neurotransmitters. It is reported that binding is stabilized by noncovalent bonds because they can be rapidly formed and broken. The neurotransmitters bind to the membrane's receptors by means of hydrogen bonds. We consider the intermolecular attraction between hydrogen atoms in a polar bond and unshared electron pair on a nearby electronegative florin, oxygen and nitrogen atoms of other molecule. That is, we study the polar H–F, H–O and H–N bonds. The dipole-dipole attractions between electronegative F, O and N with H, result in a very strong bond. Typically hydrogen bonds are formed with two or more other atoms. The energies of *symmetric* and *asymmetric* hydrogen bonds vary from 4 kJ/mol to 25 kJ/mol. The bond energies and geometry of neurotransmitters and receptors vary. For low-molecular-weight neurotransmitters (acetylcholine, γ-aminobutyric acid, catecholamines, 5-hydroxytryptamine, etc.), we found that the energy of the hydrogen-ligand complex is ~ –70 kJ/mol. Enzymatic activity, stereochemistry, geometry of coordination, interatomic distances, electrostatics, electronegativity of hydrogen-bonded systems, are the factors which significantly affect the energetics. One obtains the estimate for energy to be ~ -2×10^{-17} J per each neurotransmitter (~-1.7×10^{-17} J for acetylcholine).

Neurotransmitters are inactivated (removed from the synaptic cleft either by specific hydrolytic enzymes or by specific membrane transport proteins which uptake neurotransmitter back into either the nerve terminal or neighboring glial cells) and re-processed. Acetylcholinesterase is the enzyme which breaks acetylcholine (ACh) into choline and acetate by means of hydrolysis. It controls the rate of the reaction, and by favoring certain geometries in the transition state, lovers activation energy. We derived that the upper ehthalpy estimate for the hydrolysis reaction is ΔH=+28 kJ/mol at pH7 and 25°C. Hence, one finds 7×10^{-18} J for each hydrolized ACh molecule. The ΔH=+1.17±0.1 kJ/mol, reported in [5], results in 2.8×10^{-19} J per a single molecule.

The derived energetics of biomolecular electrochemo-mechanical transitions is with the projected solid-state microelectronic devise energetics. In particular, the energy of switching is expected to be reduced to ~1×10^{-16} J.

4. BROWNIAN DYNAMICS: MOLECULAR MOTION AND TRANSPORT

The Brownian dynamics of N particles is usually described by the second-order stochastic differential equations

$$m_i\frac{d^2\mathbf{r}_i}{dt^2}=F_v\left(\frac{d\mathbf{r}_i}{dt}\right)+\sum_{i,j}^{N}F(t,\mathbf{r}_{ij})-\frac{\partial V(\mathbf{r}_i)}{\partial\mathbf{r}_i}-\sum_{i,j}^{N}\frac{\partial V(\mathbf{r}_{ij})}{\partial\mathbf{r}_{ij}}+\boldsymbol{\xi}_i, \quad (1)$$

where m is the mass of particles; F_v is the viscous friction force, $F_v=\eta v$; η is the viscous friction coefficient; $\xi(t)$ is the Gaussian white noise, $\langle\xi(t)\rangle=0$ and $\langle\xi(t)\xi(t')\rangle=2\eta k_BT\delta(t-t')$; k_B is the Boltzmann constant; T is the absolute temperature.

We examine the stochastic particle dynamics integrating stochastic mechanical, thermal, electromagnetic, hydrodynamic, noise-induced and bistable phenomena. In three-dimensional space, the resulting translational equations of motion are derived using the displacement vector $\mathbf{r}$, velocity vector $\mathbf{v}$ ($\mathbf{v}=d\mathbf{r}/dt$), and extended state vector $\mathbf{q}$. Those $\mathbf{r}$, $\mathbf{v}$ and $\mathbf{q}$ are the state variables. One has

$$m_i\frac{d^2\mathbf{r}_i}{dt^2}=F_v\left(\frac{d\mathbf{r}_i}{dt}\right)+\sum_{i,j,n}F_n(t,\mathbf{r}_{ij})-\sum_k\frac{\partial V_k(\mathbf{r}_i)}{\partial\mathbf{r}_i}-\sum_{i,j,k}\frac{\partial V_k(\mathbf{r}_{ij})}{\partial\mathbf{r}_{ij}}+f_r(t,\mathbf{r},\mathbf{q})+\boldsymbol{\xi}_{ri},$$

$$\frac{d\mathbf{q}_i}{dt}=f_q(t,\mathbf{r},\mathbf{q})+\boldsymbol{\xi}_{qi},\ i=1,2,\ldots,N, \quad (2)$$

where $f_r(t,\mathbf{r},\mathbf{q})$ and $f_q(t,\mathbf{r},\mathbf{q})$ are the nonlinear maps.

In (2), forces $F_n(t,\mathbf{r})$ and potentials $V_k(\mathbf{r})$ of electromagnetic, hydrodynamic, thermal and other origin can be varied by changing distinct physical variables (voltage, current, temperature gradient, viscosity, etc.). Therefore, notations $V_k(\mathbf{r},\mathbf{u})$ and $F_n(t,\mathbf{r},\mathbf{u})$ are used to define the varied asymmetric potentials and forces.

For controlled particles, the equations of motion, that provides a high-fidelity translational model, are

$$m_i\frac{d^2\mathbf{r}_i}{dt^2}=F_v\left(\frac{d\mathbf{r}_i}{dt}\right)+\sum_{i,j,n}F_n(t,\mathbf{r}_{ij},\mathbf{u})-\sum_k\frac{\partial V_k(\mathbf{r}_i,\mathbf{u})}{\partial\mathbf{r}_i}-\sum_{i,j,k}\frac{\partial V_k(\mathbf{r}_{ij},\mathbf{u})}{\partial\mathbf{r}_{ij}}+f_r(t,\mathbf{r},\mathbf{q})+\boldsymbol{\xi}_{ri},$$

$$\frac{d\mathbf{q}_i}{dt}=f_q(t,\mathbf{r},\mathbf{q})+\boldsymbol{\xi}_{qi},\ i=1,2,\ldots,N. \quad (3)$$

The rotational motion is described by

$$J_i\frac{d^2\boldsymbol{\theta}_i}{dt^2}=T_v\left(\frac{d\boldsymbol{\theta}_i}{dt}\right)+\sum_{i,j,n}T_n(t,\boldsymbol{\theta}_{ij})-\sum_k\frac{\partial V_{Tk}(\boldsymbol{\theta}_i)}{\partial\boldsymbol{\theta}_i}-\sum_{i,j,k}\frac{\partial V_{Tk}(\boldsymbol{\theta}_{ij})}{\partial\boldsymbol{\theta}_{ij}}+f_\theta(t,\boldsymbol{\theta},\mathbf{q}_\theta)+\boldsymbol{\xi}_{\theta i},$$

$$\frac{d\mathbf{q}_{\theta i}}{dt}=f_\theta(t,\boldsymbol{\theta},\mathbf{q}_\theta)+\boldsymbol{\xi}_{\theta i},\ i=1,2,\ldots,N, \quad (4)$$

where $\boldsymbol{\theta}_i$ is the angular displacement, and $d\boldsymbol{\theta}_i/dt=\boldsymbol{\omega}_i$; $\boldsymbol{\omega}_i$ is the angular velocity; J_i is the moment of inertia. Other notations are similar to the translational motion.

These stochastic differential equations should be numerically solved. The linearization cannot be performed.

The particle motion is due to the time-varying applied force $F_n(t,\mathbf{r})$, potential $V_k(\mathbf{r})$, and noise $\xi(t)$. Forces can be varied and controlled, and the control vector $\mathbf{u}$ is used. The variations of $V_k(\mathbf{r},\mathbf{u})$ result in changes of $\frac{\partial V_k(\mathbf{r},\mathbf{u})}{\partial\mathbf{r}}$ which provide the force terms. Hence, the motion of Brownian

particles is controlled by the time-varying applied force $F_n(t,\mathbf{r},\mathbf{u})$ and potential $V_k(\mathbf{r},\mathbf{u})$.

The van der Waals force can be found using distinct methods. For example, using the interaction energy between spherical particles, as given as $-\frac{H}{6d_{ij}}\frac{r_i r_j}{r_i+r_j}$, one finds the force as [6-8] $F_{wij}=\frac{H}{6d_{ij}^2}\frac{r_i r_j}{r_i+r_j}$, where r_i and r_j are the radii; d_{ij} is the intersurface distance between particles; H is the Hamaker constant [9], and if $H_i \neq H_j$, the equivalent Hamaker constant is $H=(H_i H_j)^{1/2}$.

The force between a single molecule and sphere (membrane) is $F_{wmi}=-\frac{8\pi\rho_m B R_1^3 d_{mi}}{(d_{mi}-R_1)^4(d_{mi}+R_1)^4}$, where d_{mi} is the nearest distance between the center of sphere and molecule; ρ_m is density of sphere; B is the van der Waals constant.

The van der Waals interaction energy between a particle of radius r_i and a composite membrane with an outer layer with thickness h is [10]

$$E_{Wmi}=-\frac{H_i}{6}\left[r_i\left(\frac{1}{d_{mi}}-\frac{1}{d_{mi}+h}\right)-\ln\left(\frac{d_{mi}}{d_{mi}+h}\right)\right].$$

Hence, the force is found to be

$$F_{Wmi}=\frac{H_i}{6}\left[r_i\left(\frac{1}{d_{mi}^2}-\frac{1}{(d_{mi}+h)^2}\right)-\frac{h}{d_{mi}(d_{mi}+h)}\right].$$

We study the *activating information* carriers. Ions, diffused into the neuron through the membrane ionic channels, are considered to be the *regulating information* carriers. The number of ions in the synaptic cleft is defined by their concentration. Letting the ionic concentration for Na^+, Cl^-, K^+ and Ca^{2+} to be 140, 100, 5 and 2 mM, in the synaptic cleft with 25 nm separation between membranes (L=25 nm), we study the Brownian motion of 1 neurotransmitter as well as 19, 14, 1 and 1 Na^+, Cl^-, K^+ and Ca^{2+} ions.

The ions interact with a polar neurotransmitter which propagates in the synaptic cleft. We study the motion of 36 particles in three-dimensional space. This results in 324 first-order stochastic differential equations for the translational motion (3). The electric dipole moment for GABA is 4.8×10^{-29} C-m. The length of GABA is 0.91 nm. The neurotransmitter mass and diffusion coefficient are $m_{GABA}=1.71\times10^{-25}$ kg and $D_{GABA}=4\times10^{-11}$ m^2/s.

The masses, diffusion coefficients (at 37^{0}C) and ionic radii of Na^+, Cl^-, K^+ and Ca^{2+} ions used in the analysis are [2]: $m_{Na}=3.81\times10^{-26}$ kg, $m_{Cl}=5.89\times10^{-26}$ kg, $m_K=6.49\times10^{-26}$ kg, $m_{Ca}=6.66\times10^{-26}$ kg, $r_{Na}=0.95\times10^{-10}$ m, $r_{Cl}=1.81\times10^{-10}$ m, $r_K=1.33\times10^{-10}$ m, $r_{Ca}=1\times10^{-10}$ m, $D_{Na}=1.33\times10^{-9}$ m^2/s, $D_{Cl}=2\times10^{-9}$ m^2/s, $D_K=1.96\times10^{-9}$ m^2/s and $D_{Ca}=0.71\times10^{-9}$ m^2/s. The relative permittivities of presynaptic and postsynaptic membranes are $\varepsilon_{rp}=2.3$ and $\varepsilon_{rP}=2.1$.

The controlled motion of a neurotransmitter from the origin (0, 0, 0) to the binding cite (0, 0, 25 nm) is reported in Figure 2 for different simulation runs [2]. Here, L=25 nm.

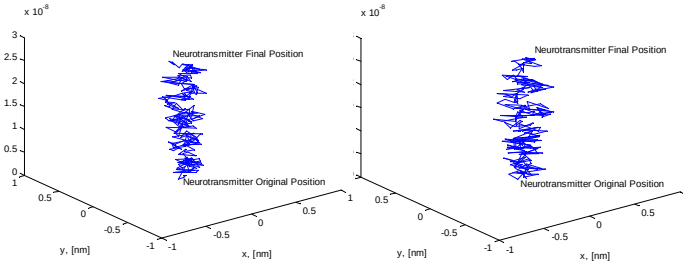

Figure 2. Controlled neurotransmitter displacement in the synaptic cleft

5. CONCLUSIONS

We reported the *fluidic* processing and interfacing devices. These developments are envisioned to be utilized in foreseen processing systems and for micro-bio interfacing. The synthesis aspects are covered. The use of biomolecules as *information* and *interfacing* carriers was introduced. It was demonstrated that the controlled motion of carriers in the fluidic cavity can be accomplished. The feasibility studies for interfacing of *fluidic* devices with *natural* cells are performed.

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