ORIGINAL RESEARCH

Proposal for Alzheimer's diagnosis using molecular buffer and bus network

S Mitatha[1]
N Moongfangklang[1]
MA Jalil[2]
N Suwanpayak[3]
T Saktioto[4]
J Ali[4]
PP Yupapin[3]

[1]Hybrid Computing Research Laboratory, King Mongkut's Institute of Technology Ladkrabang, Bangkok, Thailand; [2]Ibnu Sina Institute of Fundamental Science Studies, Nanotechnology Research Alliance, Universiti Teknologi Malaysia, Johor Bahru, Malaysia; [3]Nanoscale Science and Engineering Research Alliance (N'SERA), Advanced Research Center for Photonics, King Mongkut's Institute of Technology Ladkrabang, Bangkok, Thailand; [4]Institute of Advanced Photonics Science, Nanotechnology Research Alliance, Universiti Teknologi Malaysia, Johor Bahru, Malaysia

Correspondence: PP Yupapin
Nanoscale Science and Engineering Research Alliance (N'SERA), Advanced Research Center for Photonics, Faculty of Science, King Mongkut's Institute of Technology Ladkrabang, Bangkok 10520, Thailand
Tel +66 2 329 8414
Fax +66 2 329 8410
Email kypreech@kmitl.ac.th

Abstract: A novel design of an optical trapping tool for tangle protein (tau tangles, β-amyloid plaques) and molecular motor storage and delivery using a PANDA ring resonator is proposed. The optical vortices can be generated and controlled to form the trapping tools in the same way as the optical tweezers. In theory, the trapping force is formed by the combination between the gradient field and scattering photons, and is reviewed. By using the intense optical vortices generated within the PANDA ring resonator, the required molecular volumes can be trapped and moved dynamically within the molecular buffer and bus network. The tangle protein and molecular motor can transport and connect to the required destinations, enabling availability for Alzheimer's diagnosis.

Keywords: Alzheimer's disease, molecular diagnosis, optical trapping tool, molecular networks

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the aging population in which the loss of neural cells associated with AD is believed to be caused by the accumulation of β-amyloidal plaques.[1,2] The tangles inside neurons[3] and genes[1] are caused by abnormal axons in the neuronal networks – an important area of the brain. A study of axonal transport begins with the observation of nerve cell bodies.[4] The axon consists of many microtubules. Each microtubule is a hollow cylindrical tube with an external diameter about 25 nm and a wall thickness of approximately 4 nm. The cross section of each microtubule consists of 13 proto-filaments with the fastest axonal transport occurring at a velocity of 5 μm per second.[5] The main mechanism is to deliver cellular components to their action site, which is long-range microtubule-based transport. The major components of the transport machinery are the "engines", or molecular motors.

In AD, the link protein is affected by disease disturbing the axonal transportation.[6] The microtubules in the axon are more resistant to the severing protein katanin than microtubules in other parts of the neuron. The sustained loss of tau from axonal microtubules over time renders them more sensitive to endogenous severing proteins. Thus, it causes the microtubule array to gradually disintegrate in tauopathies such as AD.[7–9] The optical trapping tool was first invented by Ashkin et al.[10] It has emerged as a powerful tool with broad-reaching applications in biology, physics, engineering, and medicine. The ability of optical trapping and manipulation of viruses, living cells, bacteria, and organelles by laser radiation pressure without damage[11,12] has

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been demonstrated,[13,14] and is of particular interest in the fields of medicine and nanotechnology. The possibility of liquids transportation and delivery at the nanoscale has been rapidly developed within the capillary or microchannel.[15] Micronanofluidics is a multi-dimensional field of science functioning in the 1–100 nm range.[15] It is a burgeoning field with important applications in areas such as medical devices, biotechnology, chemical synthesis, and analytical chemistry.[16]

Researchers have used this promising technique in the study of optical trapping applications such as the control of kinesin movement on the microtubule surface[17–19] to the axon terminal. In the study of micronanofluidics combined with optics, Erickson laboratory researchers'[20–24] interests include advancing flows, delivery, and implantable devices in living organs.[25–27] New advances in optics strategy using light to drive and halt neuronal activity with molecular specificity have been investigated. Moreover, the optical methods that have been developed to date encompass a broad array of strategies, including photorelease of caged neurotransmitters, engineered light-gated receptors and channels, naturally light-sensitive ion channels and pumps,[28] and artificial neural networks.[29] Recently, the use of optical trapping tool microscopic volume transportation within an add/drop multiplexer has been reported both in theory[30] and experimentally.[31] Here the transporter is known as an optical tweezer. The optical tweezer generation technique is used as a powerful tool for the manipulation of micrometer-sized particles. To date, the useful static tweezers are well recognized and realized. The use of dynamic tweezers is now also realized in practical work.[32–34] Schulz et al[35] have shown the possibility of trapped atoms being transferred between two optical potentials. In principle, an optical tweezer uses the forces exerted by intensity gradients in the strongly focused beams of light to trap and move the microscopic volumes of matter via a combination of forces induced by the interaction between photons, due to the photon scattering effects. In application, the field intensity can be adjusted and tuned to the desired gradient field. The scattering force can then form the suitable trapping force. Hence, the appropriate force can be configured as the transmitter/receiver for performing a long distance microscopic transportation.

In this paper, the dynamic optical tweezers/vortices are generated using the optical pulse propagating within an add/drop optical multiplexer incorporating two nanoring resonators (PANDA ring resonator), and using light pulse control within an add/drop optical filter.[36] By using the proposed system, the tangle protein and molecular motor can be trapped, transported, and received into the optical waveguide by optical tweezers. By utilizing the reasonable optical pulse input power, the dynamic tweezers can be controlled and stored within the system before reaching the desired destinations via the molecular buffer and bus network. In application, the neuron network can be connected by the link protein that can be available for AD and recovery, which will be discussed in detail.

Theoretical background

In theory, the trapping forces are exerted by the intensity gradients in the strongly focused beams of light to trap and move the microscopic volumes of matter, in which the optical forces are customarily defined by the following relationship:[37]

$$F = \frac{Q n_m P}{c} \qquad (1)$$

where Q is a dimensionless efficiency, n_m is the refractive index of the suspending medium, c is the speed of light, and P is the incident laser power, measured at the specimen. Q represents the fraction of power utilized to exert force. For a plane wave that is incident on a perfectly absorbing particle, Q is equal to 1. To achieve stable trapping, the radiation pressure must create a stable, three-dimensional equilibrium. Because biological specimens are usually contained in aqueous medium, the dependence of F on n_m can rarely be exploited to achieve higher trapping forces. Increasing the laser power is possible, but only over a limited range due to the possibility of optical damage. Q itself is therefore the main determinant of trapping force. It depends upon the NA (numerical aperture), laser wavelength, light polarization state, laser mode structure, relative index of refraction, and geometry of the particle.

In the Rayleigh regime, trapping forces decompose naturally into two components. Since, at this limit, the electromagnetic field is uniform across the dielectric, particles can be treated as induced point dipoles. The scattering force is given by:[37]

$$F_{scatt} = n_m \frac{\langle S \rangle \sigma}{c}, \qquad (2)$$

where

$$\sigma = \frac{8}{3} \pi (kr)^4 r^2 \left(\frac{m^2 - 1}{m^2 + 2} \right)^2 \qquad (3)$$

Here σ is the scattering cross section of a Rayleigh sphere with radius r. $\langle S \rangle$ is the time averaged Poynting vector, n is the index of refraction of the particle, $m = n/n_m$ is the relative index, and $k = 2\pi n_m /\lambda$ is the wave number of the light. The scattering force is proportional to the energy flux and points along the direction of propagation of the incident light. The gradient field (F_{grad}) is the Lorentz force acting on the dipole induced by the light field. It is given by:[37]

$$F_{grad} = \frac{\alpha}{2} \nabla \left\langle E^2 \right\rangle, \qquad (4)$$

where

$$\alpha = n_m^2 r^3 \left(\frac{m^2 - 1}{m^2 + 2} \right) \qquad (5)$$

is the polarizability of the particle. The gradient force is proportional and parallel to the gradient in energy density (for $m > 1$). The large gradient force is formed by the large depth of the laser beam. Stable trapping requires that the gradient force is in the $-\hat{z}$ direction, which is against the direction of incident light (dark soliton valley) and greater than the scattering force. By increasing the NA, when the focal spot size is decreased, the gradient strength is increased.[38] These occur within a tiny system, for instance, a nanoscale device such as the nanoring resonator.

Alzheimer's diagnosis using molecular network

In operation, the optical tweezers can be trapped, transported, and stored within the PANDA ring resonator and wavelength router, which can be used to form the microscopic volume (molecular motor, tau tangles, and β-amyloids plaques) transportation, and drug delivery via the waveguide.[39] The manipulation of trapped and removed tangle proteins within the optical tweezers has been reported. Optical trapping is one of the most powerful single-molecule techniques with wide reaching applications in medicine. Living cells and important biological applications can be investigated using optical tweezers.[40] Hosokawa et al[41] have demonstrated the optical trapping of synaptic vesicles in a hippocampal neuron and found that the intracellular synaptic vesicles can be trapped at the focal spot within the laser irradiation time. This occurs because the vesicles form clusters in neurons, and are effectively trapped at the focal spot due to its high polarizability.

In this paper, we propose the use of the optical trapping tools for removing tangle protein and transportation out of neuronal cells, which induces the neurofibrillary degeneration caused by AD. Amyloid and tau proteins are both implicated in memory impairment, mild cognitive impairment (MCI), and early AD, however their interaction is unknown.[42] In operation, the optical tweezer can be trapped, transported, and stored within the PANDA ring resonator,[30] incorporating a wavelength router in the same drug-delivery network system.[7] We used the theory of optical trapping and transportation technique[43–45] to trap kinesins for the manipulation of synaptic vesicles in critical areas of the neuronal network; processing and removing the amyloid plaques to prevent the accumulation of them between nerve cells in the brain. The spherical kinesin motor molecules are directly moved on to the microtubules where they could be activated by ATP,[40] which is activated by the interaction of nerve cells to each other.

The proposed AD system is as shown in Figure 1. By using the molecular buffer and bus network, the required trapped volumes can be transported within the network to the required destinations. The trapped tangle protein can be filtered via the add/drop filter before reaching the desired destinations. The throughput port (Et1) output of the add/drop filter is connected to the axon, in which the effective area of the waveguide is 2.01 μm^2 (r = 800 nm) and the outside diameter of the microtubule is 25 nm.[5] The diameter of axons at birth is 1 μm, increasing through childhood (7 years) to 12 μm, and later to 24 μm in adulthood.[46] The optical tool is connected to the axon and between the nerve cells to trap the tangle protein into the removal storage by an add/drop filter (control port), otherwise, the bus network is designed to trap the molecular motor to activate the information of the neuronal cell at the same time. Figure 2 shows a schematic of the waveguide and microtubule position in the axon. The proposed design system is used to trap kinesin[47] and moves/stores the tangle protein via the molecular buffer and bus network. The light waveguide is inserted into the axon to trap the kinesin and traps/stores/receives the tangle protein. The ungrouped form of these proteins causes Alzheimer's disease.[48] The optical tweezer can induce the mechanical unfolding and refolding of a single protein molecule in the absence and the presence of molecular chaperones.[49] Moreover, this noninvasive optical trapping technique can be used to unfold the poly-protein[50] in adult neurons.[51]

In simulation, the bright soliton with center wavelength at 1.50 μm, peak power 2 W, pulse 35fs is input into the
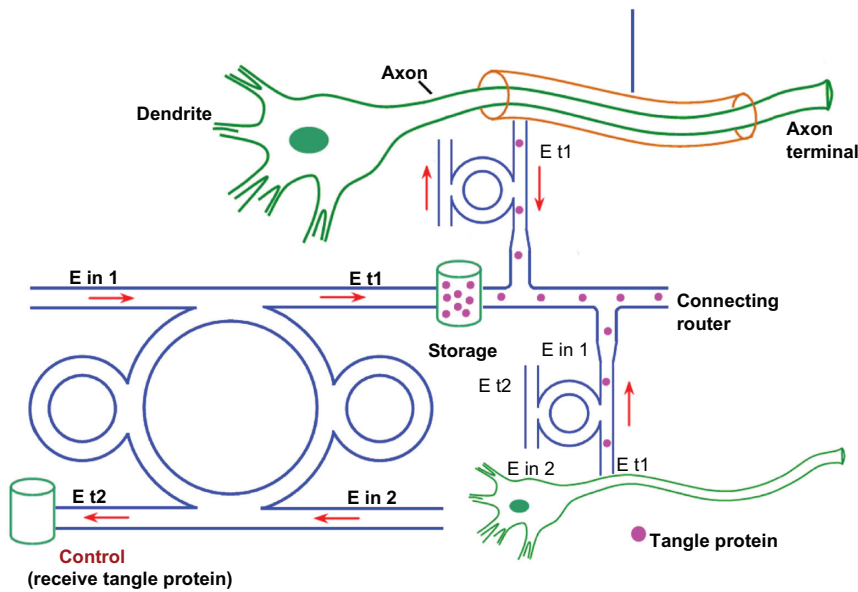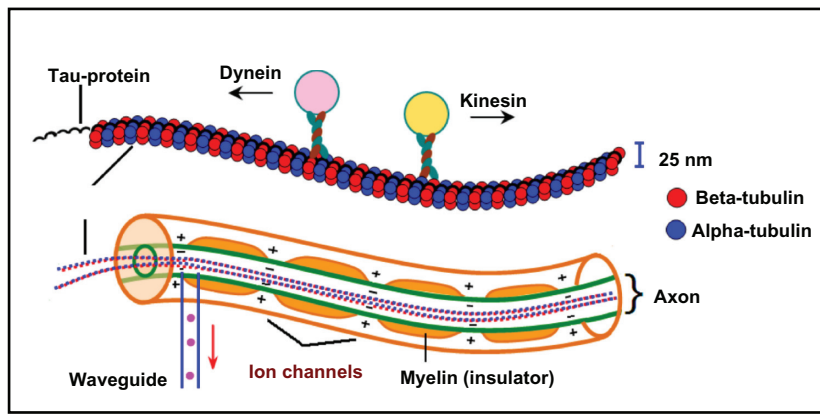
Figure 1 Schematic diagram of an Alzheimer's diagnosis system using a molecular buffer and bus network.

system via the input port. The coupling coefficients are given as $\kappa_0 = 0.5$, $\kappa_1 = 0.35$, $\kappa_2 = 0.1$, and $\kappa_3 = 0.35$, respectively. The ring radii are $R_{ad} = 20$ and $1\ \mu m$, $R_R = 5\ \mu m$ and $0.8\ \mu m$, and $R_L = 5$ and $0.8\ \mu m$, respectively. To date, the evidence of a practical device with radius of approximately $0.8\ \mu m$ has been reported by the authors[52] in which A_{eff} is
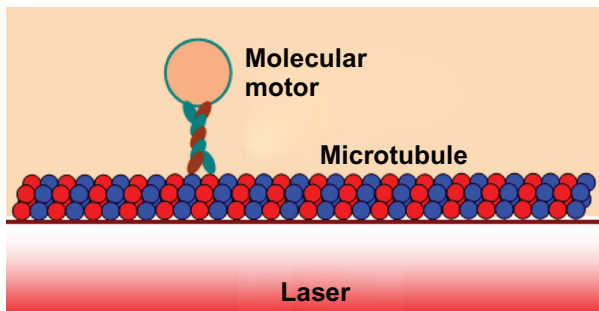
Figure 2 Schematic of microtubule and optical waveguide position in the axon.

$2.01\ \mu m^2$ ($r = 800$ nm). In this case, the dynamic tweezers (gradient fields) can be in the forms of bright solitons, Gaussian pulses, and dark solitons, which can be used to trap the required tangle protein. In Figure 3, there are four different center wavelengths of tweezers generated, where the dynamical movements are (a) $|E_1|^2$, (b) $|E_2|^2$, (c) $|E_3|^2$, (d) $|E_4|^2$, (e) through port, and (f) drop port signals, where in this case all microscopic volumes are received by the drop port. In practice, the fabrication parameters that can be easily controlled are the ring resonator radii instead of coupling constants. The important aspect of the result is that the tunable tweezers can be obtained by tuning (controlling) the add (control) port input signal, in which the required number of single protein (tau-protein/beta myeloid, plaque) can be obtained and seen at the drop/through ports. Otherwise, they propagate within a PANDA ring before collapsing/decaying into the waveguide.
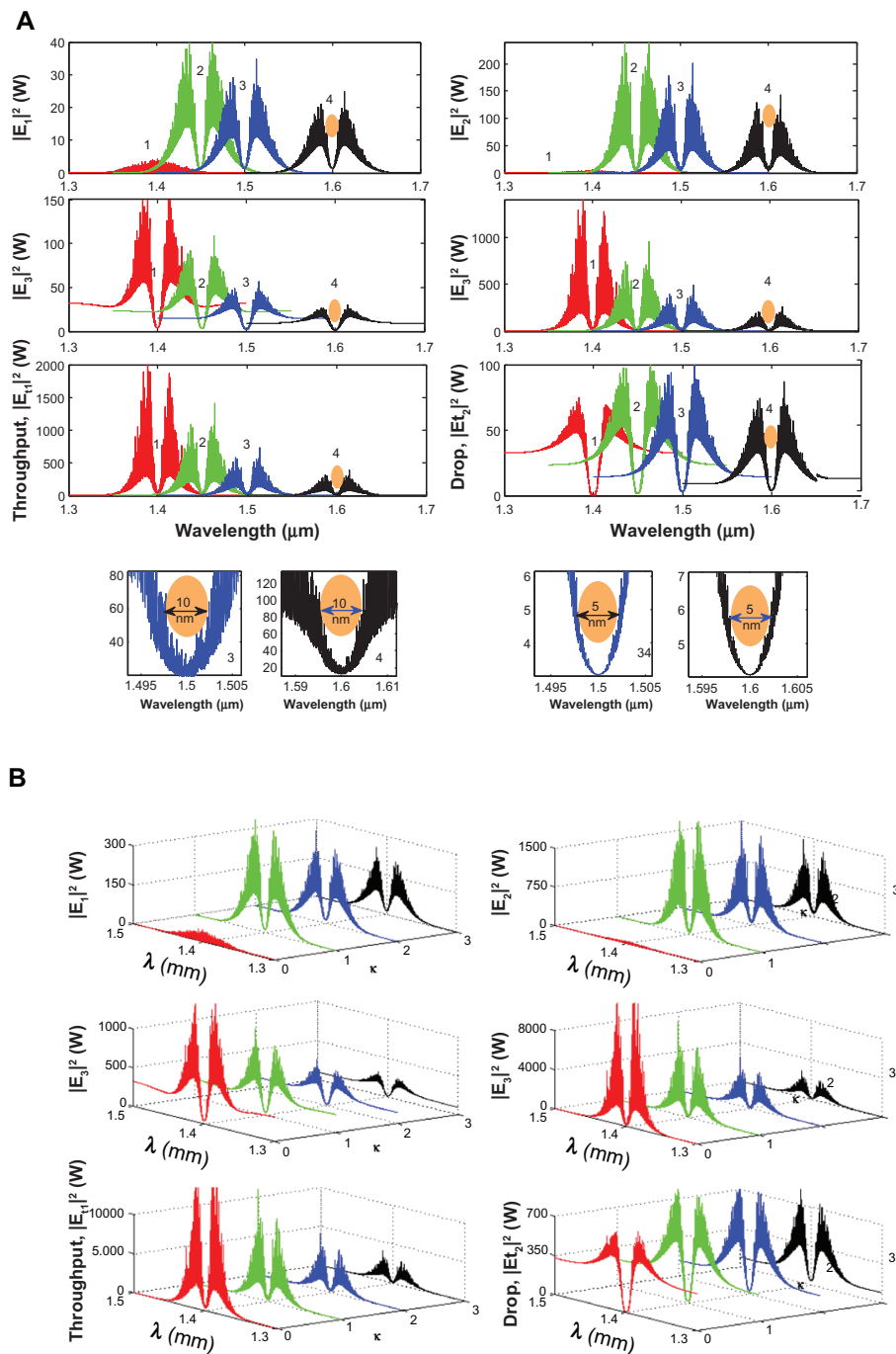
Figure 3 Result of the dynamic tweezers within the buffer with different (**A**) wavelengths and (**B**) coupling constants, where $R_{ad} = 20$ μm, $R_R = R_L = 5$ μm.

More results of the optical tweezers generated within the PANDA ring are shown in Figure 4, where in this case the bright soliton is used as the control port signal to obtain the tunable results. The output optical tweezers of the through and drop ports with different coupling constants are shown in Figure 4A, while the different wavelength results are shown in Figure 4B, which is allowed to form the selected targets. In application, the trapped microscopic volumes (molecules) can transport into the wavelength router via the through port, while the retrieved microscopic volumes are received via the drop port (connecting target). The advantage of the proposed system is that the transmitter and receiver can be fabricated on-chip and alternatively operated by a single device.
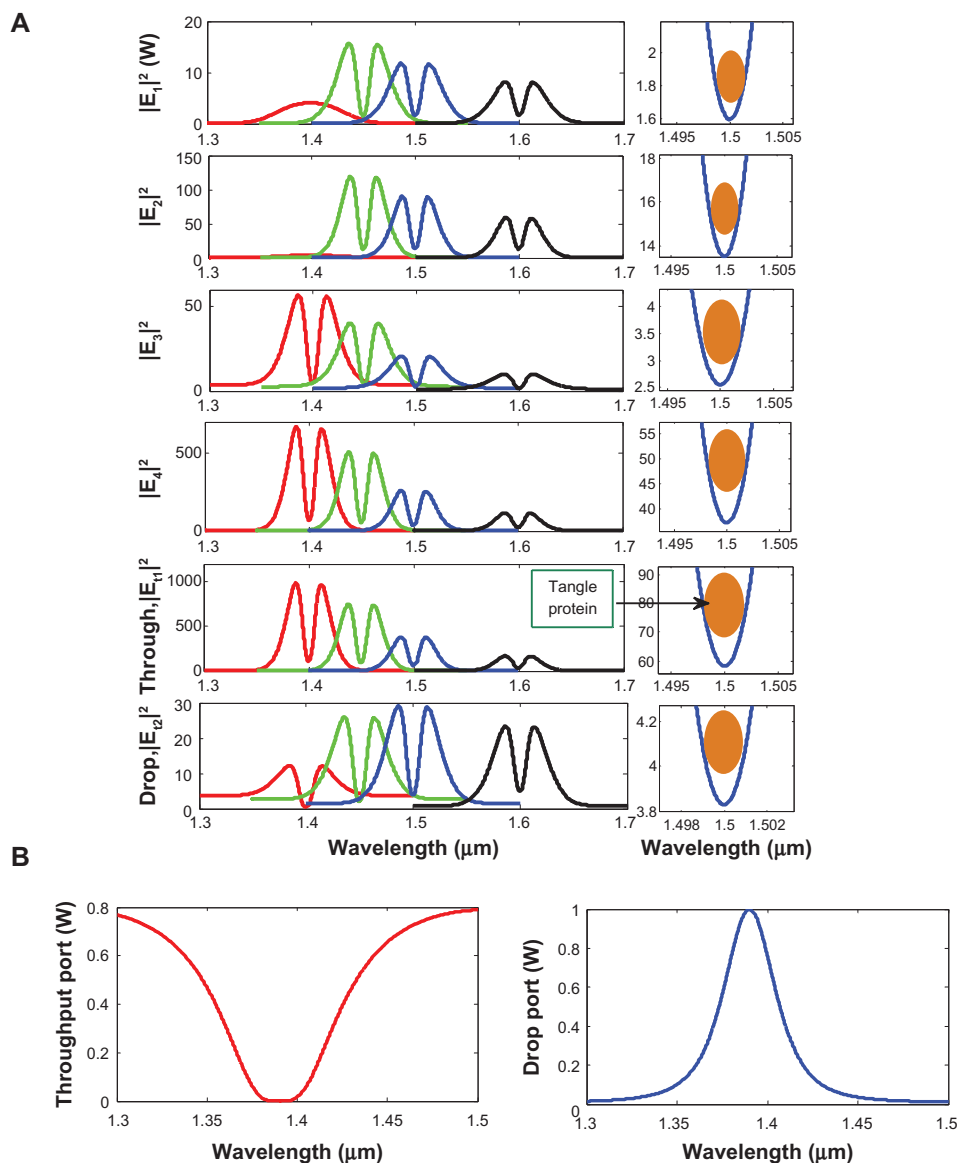
Figure 4 Result of the dynamic tweezers within the buffer with different (**A**) coupling constants and (**B**) The optical potential well of throughput and norm of drop port, where R_{ad} = 1 µm, R_R = R_L = 800 nm.

Conclusion

Tau protein and β-amyloid deposits are known as the targets in Alzheimer's disease. Recent studies show tau as a potential diagnostic marker and a candidate for change and maintenance via drug application.[53–55] In this work, we propose the future design of Alzheimer's therapy in that the tangle protein and molecular motor can be trapped, transported, and received into the optical waveguide by optical tweezers. By utilizing the reasonable optical pulse input power, the dynamic tweezers can be controlled and stored within the system before reaching the final destination via the molecular buffer and bus network. The tweezer can also be amplified by using the nanoring resonators and modulated signals via the control port. In conclusion, we have shown that the use of the molecular buffer and bus network for long distance protein trapping and transportation can be realized by using the proposed system. The trapped volumes or molecules are then transported via the wavelength router and bus network to the required (connecting) targets, and are applicable to AD. However, the large microscopic volumes and networks are potential problems, and the search for a new guide pipe medium,[40] such as nano tubes and crosstalk effects will be the next topic of investigation.

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Disclosure

No conflicts of interest were declared in relation to this paper.

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