

Fighting against fast speckle decorrelation for light focusing inside live tissue by photon frequency shifting

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S1: Mathematical description of light focusing inside tissue by binary-phase DOPC

To describe the whole process of binary-phase DOPC mathematically, we used column vectors to express all the optical fields. $\mathbf{E}_{\text{mod}} = \mathbf{E}_{\text{GS}} + \mathbf{E}_0$ is the optical field on the plane immediately after the guide star, where \mathbf{E}_{GS} is the component with the modulation of the guide star, and \mathbf{E}_0 is the unmodulated component. \mathbf{E}_{GS} will be transformed from \mathbf{E}_{GS1} to \mathbf{E}_{GS2} with the state switching of the guide star. All the optical fields contain J complex elements. Here, we set the first element of \mathbf{E}_{GS} as the position the guide star. Thus, \mathbf{E}_{GS} can be expressed as:

$$\mathbf{E}_{\text{GS}} = (E_{\text{GS}}, 0, \dots, 0)_{J \times 1}^T, \quad (\text{S1})$$

where “ T ” stands for the transpose operator, and E_{GS} changes from E_{GS1} to E_{GS2} when the state of the guide star is switched. The optical field of the scattered light on the plane of the camera can be written as

$$\mathbf{E}_{\text{scattered}} = \mathbf{T} \cdot \mathbf{E}_{\text{mod}} = \mathbf{T} \cdot (\mathbf{E}_{\text{GS}} + \mathbf{E}_0). \quad (\text{S2})$$

where \mathbf{T} is the transmission matrix of the tissue and can be expressed as a $M \times J$ complex matrix whose element $t_{mj} = C_{mj} \exp(i\varphi_{mj})$, $m = 1, \dots, M$, $j = 1, \dots, J$ follows a circular Gaussian distribution, C_{mj} follows a Rayleigh distribution, φ_{mj} follows a uniform distribution within the range of $[0, 2\pi)$, and $\mathbf{E}_{\text{scattered}}$ is a column vector of M elements. The m -th element of $\mathbf{E}_{\text{scattered}}$ is $E_{\text{scattered}}^{(m)} = E_{\text{TGS}}^{(m)} + E_{\text{TE0}}^{(m)}$, where $E_{\text{TGS}}^{(m)}$ and $E_{\text{TE0}}^{(m)}$ are the m -th element of $\mathbf{T} \cdot \mathbf{E}_{\text{GS}}$ and $\mathbf{T} \cdot \mathbf{E}_0$, respectively. Accordingly, $\mathbf{E}_{\text{scattered}}$ will be changed from $\mathbf{E}_1 = \mathbf{T} \cdot (\mathbf{E}_{\text{GS1}} + \mathbf{E}_0)$ to $\mathbf{E}_2 = \mathbf{T} \cdot (\mathbf{E}_{\text{GS2}} + \mathbf{E}_0)$ when the state of the guide star is switched, and the field perturbation between \mathbf{E}_1 and \mathbf{E}_2 is $\Delta \mathbf{E} = \mathbf{E}_1 - \mathbf{E}_2$.

With the interference of $\mathbf{E}_{\text{scattered}}$ and \mathbf{E}_{R} , the optical field of the reference beam, a hologram is generated on the camera. Assume that \mathbf{E}_{R} is a plane wave, and all the elements have the same expression of $E_{\text{R}} = A_{\text{R}} \exp(i\varphi_{\text{R}})$, where A_{R} and φ_{R} are the amplitude and initial phase, respectively. Then, the m -th element of the hologram \mathbf{I}_{holo} is obtained as

$$\begin{aligned} I_{\text{holo}}^{(m)} &= \left(E_{\text{TGS}}^{(m)} + E_{\text{TE0}}^{(m)} + E_{\text{R}} \right) \times \left(E_{\text{TGS}}^{(m)} + E_{\text{TE0}}^{(m)} + E_{\text{R}} \right)^* \\ &= E_{\text{TGS}}^{(m)} E_{\text{TGS}}^{(m)*} + E_{\text{R}} E_{\text{R}}^* + E_{\text{TE0}}^{(m)} E_{\text{TE0}}^{(m)*} \\ &\quad + 2\text{real} \left(E_{\text{TGS}}^{(m)} E_{\text{R}}^* + E_{\text{TGS}}^{(m)} E_{\text{TE0}}^{(m)*} + E_{\text{R}} E_{\text{TE0}}^{(m)*} \right), \end{aligned} \quad (\text{S3})$$

where $\text{real}(\cdot)$ denotes the real part of a complex number. By differentiating the two holograms with

different guide star states, the m -th element of the differential hologram $\Delta \mathbf{I}_{\text{holo}}$ is computed as

$$\Delta I_{\text{holo}}^{(m)} = 2\text{real} \left[\Delta E_{\text{TGS}}^{(m)} \left(E_{\text{R}}^* + E_{\text{TE0}}^{(m)*} \right) \right]. \quad (\text{S4})$$

where ΔE_{TGS} is the field difference, and $\Delta E_{\text{TGS}}^{(m)}$ is the m -th element of ΔE_{TGS} . In our experiments, since the amplitude of E_{R} is much larger than that of $E_{\text{TE0}}^{(m)}$, Eq. (S4) can be simplified as

$$\Delta I_{\text{holo}}^{(m)} = 2\text{real} \left(\Delta E_{\text{TGS}}^{(m)} E_{\text{R}}^* \right) = 2\text{real}(t_{m1} \Delta E_{\text{GS}} E_{\text{R}}^*). \quad (\text{S5})$$

where $\Delta E_{\text{GS}} = E_{\text{GS1}} - E_{\text{GS2}}$. Assuming that $\Delta E_{\text{GS}} = A_{\text{GS}} \exp(i\varphi_{\text{GS}})$, and substituting $t_{mj} = C_{mj} \exp(i\varphi_{mj})$, and $E_{\text{R}} = A_{\text{R}} \exp(i\varphi_{\text{R}})$ into Eq. (S5), we obtained that

$$\begin{aligned} \Delta I_{\text{holo}}^{(m)} &= 2\text{real} \{ C_{m1} A_{\text{GS}} A_{\text{R}} \exp[i(\varphi_{m1} + \varphi_{\text{GS}} - \varphi_{\text{R}})] \} \\ &= 2C_{m1} A_{\text{GS}} A_{\text{R}} \cos(\varphi_{m1} + \varphi_{\text{GS}} - \varphi_{\text{R}}). \end{aligned} \quad (\text{S6})$$

By thresholding all the elements of $\Delta \mathbf{I}_{\text{holo}}$ at zero, a binary conjugated phase map $\boldsymbol{\varphi}_{\text{SLM}}$ displayed on a spatial light modulator (SLM) located at the conjugated position of the camera is obtained, whose m -th element is

$$\varphi_{\text{SLM}}^{(m)} = \begin{cases} 0, & \text{if } \Delta I_{\text{holo}}^{(m)} \geq 0, \text{ i.e., } -\pi/2 + 2k\pi \leq (\varphi_{m1} + \varphi_{\text{GS}} - \varphi_{\text{R}}) \leq \pi/2 + 2k\pi \\ \pi, & \text{if } \Delta I_{\text{holo}}^{(m)} < 0, \text{ i.e., } \pi/2 + 2k\pi < (\varphi_{m1} + \varphi_{\text{GS}} - \varphi_{\text{R}}) < 3\pi/2 + 2k\pi \end{cases}. \quad (\text{S7})$$

where $k = 1, 2, 3, \dots$ is an integer. Subsequently, a playback beam with an optical field of $\mathbf{E}_{\text{playback}}$ is achieved by modulating the reference beam with the computed phase map $\boldsymbol{\varphi}_{\text{SLM}}$ as follows:

$$\mathbf{E}_{\text{playback}} = A_{\text{R}} \exp(i\varphi_{\text{R}}) \exp(i\boldsymbol{\varphi}_{\text{SLM}}). \quad (\text{S8})$$

When $\mathbf{E}_{\text{playback}}$ propagates back through the tissue, on the guide-star plane, the optical field can be obtained by multiplying the backward transmission matrix \mathbf{T}^T as

$$\begin{aligned} \mathbf{E}_{\text{OPC}} &= \mathbf{T}^T \mathbf{E}_{\text{playback}} \\ &= A_{\text{R}} \exp(i\varphi_{\text{R}}) \mathbf{T}^T \exp[i\boldsymbol{\varphi}_{\text{SLM}}], \end{aligned} \quad (\text{S9})$$

whose j -th element is

$$E_{\text{OPC}}^{(j)} = A_{\text{R}} \exp(i\varphi_{\text{R}}) \sum_{m=1}^M C_{mj} \exp(i\varphi_{mj}) \exp(i\varphi_{\text{SLM}}^{(m)}). \quad (\text{S10})$$

At the position where the guide star resides ($j = 1$), the optical field is

$$E_{\text{OPC}}^{(1)} = A_{\text{R}} \exp(i\varphi_{\text{R}}) \sum_{m=1}^M C_{m1} \exp \left[i(\varphi_{m1} + \varphi_{\text{SLM}}^{(m)}) \right]. \quad (\text{S11})$$

According to Eq. (S7), $\varphi_{m1} + \varphi_{\text{SLM}}^{(m)}$ is always in the region of $[-\pi/2 - \varphi_{\text{GS}} + \varphi_{\text{R}} + 2k\pi, \pi/2 - \varphi_{\text{GS}} + \varphi_{\text{R}} + 2k\pi]$. Thus, photons modulated by different SLM pixels interfere constructively to form a focus at the position of the guide star. In contrast, at those positions outside the guide star ($j \neq 1$), photons interfere randomly with each other.

S2: Enhancing the quality of the light focusing by fast DOPC

When fast physiological motions exist, we decomposed $E_{\text{TE0}}^{(m)}$ into two parts, $E_{\text{TE0}}^{(m)} = E_{\text{D}}^{(m)} + E_{\text{S}}^{(m)}$, where $E_{\text{D}}^{(m)}$ is the component of fast tissue decorrelation that changes during the process of DOPC and $E_{\text{S}}^{(m)}$ is a stable component that does not vary during this process. Then, we rewrote Eq. (S3) as

$$\begin{aligned} I_{\text{holo}}^{(m)} &= \left(E_{\text{TGS}}^{(m)} + E_{\text{S}}^{(m)} + E_{\text{D}}^{(m)} + E_{\text{R}} \right) \times \left(E_{\text{TGS}}^{(m)} + E_{\text{S}}^{(m)} + E_{\text{D}}^{(m)} + E_{\text{R}} \right)^* \\ &= E_{\text{TGS}}^{(m)} E_{\text{TGS}}^{(m)*} + E_{\text{R}} E_{\text{R}}^* + E_{\text{S}}^{(m)} E_{\text{S}}^{(m)*} + E_{\text{D}}^{(m)} E_{\text{D}}^{(m)*} + 2\text{real} \left(E_{\text{TGS}}^{(m)} E_{\text{S}}^{(m)*} \right. \\ &\quad \left. + E_{\text{TGS}}^{(m)} E_{\text{D}}^{(m)*} + E_{\text{TGS}}^{(m)} E_{\text{R}}^* + E_{\text{D}}^{(m)} E_{\text{S}}^{(m)*} + E_{\text{S}}^{(m)} E_{\text{R}}^* + E_{\text{D}}^{(m)} E_{\text{R}}^* \right). \end{aligned} \quad (\text{S12})$$

By differentiating the two holograms with different guide star states, the m -th element of the differential hologram ΔI_{holo} is computed as

$$\begin{aligned} \Delta I_{\text{holo}}^{(m)} &= 2\text{real} \left[\Delta E_{\text{TGS}}^{(m)} \left(E_{\text{S}}^{(m)*} + E_{\text{D}}^{(m)*} + E_{\text{R}}^* \right) + \right. \\ &\quad \left. \Delta E_{\text{D}}^{(m)} \left(E_{\text{S}}^{(m)*} + E_{\text{R}}^* \right) \right], \end{aligned} \quad (\text{S13})$$

where $\Delta E_{\text{D}}^{(m)}$ is the variation of $E_{\text{D}}^{(m)}$ during the acquisition of the two holograms and the components that don't change over time is eliminated. Since the amplitude of E_{R} is much larger than that of $E_{\text{TGS}}^{(m)}$, $E_{\text{S}}^{(m)}$ and $E_{\text{D}}^{(m)}$ in our experiments, Eq. (S13) was simplified to

$$\Delta I_{\text{holo}}^{(m)} = 2\text{real} \left(\Delta E_{\text{TGS}}^{(m)} E_{\text{R}}^* \right) + 2\text{real} \left(\Delta E_{\text{D}}^{(m)} E_{\text{R}}^* \right). \quad (\text{S14})$$

In general, the amplitude of $\Delta E_{\text{D}}^{(m)}$ increases when the time interval between adjacent hologram capture increases. Fast DOPC reduces this time interval to shorter than the decorrelation time of fast physiological motions, so that the impact of $2\text{real} \left(\Delta E_{\text{D}}^{(m)} E_{\text{R}}^* \right)$ on light focusing is minimized.

S3: Mathematical description of light focusing inside tissue by PFM-DOPC

According to Eq. (4) in main text, $\mathbf{E}_{\text{mod}} = \mathbf{E}_{-1} + \mathbf{E}_0 + \mathbf{E}_{+1}$, where \mathbf{E}_{-1} and \mathbf{E}_{+1} are the guide star modulation components with shifted frequencies of $-f_{\text{mod}}$ and f_{mod} , respectively, and \mathbf{E}_0 is the

component without modulation. We assume that the first element is the position of the guide star, then \mathbf{E}_{-1} and \mathbf{E}_{+1} can be expressed as

$$\mathbf{E}_{-1} = (E_{-1}, 0, \dots, 0)_{J \times 1}^T, \quad (\text{S15})$$

and

$$\mathbf{E}_{+1} = (E_{+1}, 0, \dots, 0)_{J \times 1}^T. \quad (\text{S16})$$

According to Eq. (3) in the main text, it can be obtained that

$$E_{-1} = AB_{-1} \exp\{i[-2\pi(f_0 - f_{\text{mod}})t + \varphi_0]\}, \quad (\text{S17})$$

and

$$E_{+1} = AB_{+1} \exp\{i[-2\pi(f_0 + f_{\text{mod}})t + \varphi_0]\}. \quad (\text{S18})$$

According to Eq. (4) in the main text, B_{-1} and B_{+1} can be expressed as $B \cdot \exp(-i\varphi_b)$ and $B \cdot \exp(i\varphi_b)$, respectively, where B is real.

After passing through a scattering medium, the optical field of the scattered light on the camera plane can be calculated as

$$\mathbf{E}_{\text{scattered}} = \mathbf{T} \cdot \mathbf{E}_{\text{mod}} = \mathbf{T} \cdot (\mathbf{E}_{-1} + \mathbf{E}_{+1}) + \mathbf{T} \cdot \mathbf{E}_0. \quad (\text{S19})$$

The m -th element of $\mathbf{E}_{\text{scattered}}$ is $E_{\text{scattered}}^{(m)} = E_{\text{TE0}}^{(m)} + E_{\text{G}}^{(m)}$, where $E_{\text{TE0}}^{(m)}$ is the m -th element of $\mathbf{T} \cdot \mathbf{E}_0$ and $E_{\text{G}}^{(m)}$ is the m -th element of $\mathbf{T} \cdot (\mathbf{E}_{-1} + \mathbf{E}_{+1})$. Since the reference beam \mathbf{E}_{R} is a plane wave, all the elements can be expressed as $E_{\text{R}} = A_{\text{R}} \exp[i(-2\pi f_0 t + \varphi_{\text{R}})]$, where A_{R} is the amplitude and φ_{R} is the initial phase. When $\mathbf{E}_{\text{scattered}}$ interferes with \mathbf{E}_{R} , the m -th element of the hologram is

$$\begin{aligned} I_{\text{holo}}^{(m)} &= \left(E_{\text{G}}^{(m)} + E_{\text{TE0}}^{(m)} + E_{\text{R}} \right) \times \left(E_{\text{G}}^{(m)} + E_{\text{TE0}}^{(m)} + E_{\text{R}} \right)^* \\ &= E_{\text{G}}^{(m)} E_{\text{G}}^{(m)*} + E_{\text{R}} E_{\text{R}}^* + E_{\text{TE0}}^{(m)} E_{\text{TE0}}^{(m)*} \\ &\quad + 2\text{real}\left(E_{\text{G}}^{(m)} E_{\text{R}}^* + E_{\text{G}}^{(m)} E_{\text{TE0}}^{(m)*} + E_{\text{R}} E_{\text{TE0}}^{(m)*} \right), \end{aligned} \quad (\text{S20})$$

We differentiated two holograms captured with a starting time of t_0 and a time interval of $1/(2f_{\text{mod}})$, then a differential hologram can be obtained with the m -th element as

$$\begin{aligned} \Delta I_{\text{holo}}^{(m)} &= I_{\text{holo}}^{(m)} \Big|_{t=t_0} - I_{\text{holo}}^{(m)} \Big|_{t=t_0+1/(2f_{\text{mod}})} \\ &= 2\text{real}\left(E_{\text{G}}^{(m)} E_{\text{R}}^* + E_{\text{G}}^{(m)} E_{\text{TE0}}^{(m)*} \right) \Big|_{t=t_0} \\ &\quad - 2\text{real}\left(E_{\text{G}}^{(m)} E_{\text{R}}^* + E_{\text{G}}^{(m)} E_{\text{TE0}}^{(m)*} \right) \Big|_{t=t_0+1/(2f_{\text{mod}})}. \end{aligned} \quad (\text{S21})$$

In our experiments, the amplitude of $E_{\text{TE0}}^{(m)}$ is much smaller than that of E_{R} , thus Eq. (S21) can be simplified to

$$\Delta I_{\text{holo}}^{(m)} = 2\text{real}\left(E_{\text{G}}^{(m)} E_{\text{R}}^*\right)\Big|_{t=t_0} - 2\text{real}\left(E_{\text{G}}^{(m)} E_{\text{R}}^*\right)\Big|_{t=t_0+1/(2f_{\text{mod}})}. \quad (\text{S22})$$

by neglecting $E_{\text{G}}^{(m)} E_{\text{TE0}}^{(m)*}$. According to Eqs. (S15–S19), we obtain

$$\begin{aligned} E_{\text{G}}^{(m)} &= ABt_{m1} \exp(i\varphi_0) \left(\exp\{i[-2\pi(f_0 - f_{\text{mod}})t - \varphi_{\text{b}}]\} \right. \\ &\quad \left. + \exp\{i[-2\pi(f_0 + f_{\text{mod}})t + \varphi_{\text{b}}]\} \right) \\ &= ABC_{m1} \exp[i(\varphi_{m1} + \varphi_0)] \left(\exp\{i[-2\pi(f_0 - f_{\text{mod}})t - \varphi_{\text{b}}]\} \right. \\ &\quad \left. + \exp\{i[-2\pi(f_0 + f_{\text{mod}})t + \varphi_{\text{b}}]\} \right). \end{aligned} \quad (\text{S23})$$

By substituting Eq. (S23) into Eq. (S22), it can be obtained that

$$\begin{aligned} \Delta I_{\text{holo}}^{(m)} &= ABC_{m1} A_{\text{R}} A_{\text{add}} \cos(2\pi f_{\text{mod}} t_0 - \varphi_{\text{b}}) \times \\ &\quad \cos(\varphi_{m1} + \varphi_0 - \varphi_{\text{R}} + \varphi_{\text{add}}). \end{aligned} \quad (\text{S24})$$

where A_{add} and φ_{add} are two constants determined by f_0, f_{mod} and t_0 . By thresholding $\Delta I_{\text{holo}}^{(m)}$ at zero, a binary phase map $\boldsymbol{\varphi}_{\text{SLM}}$ is obtained, whose m -th element is

$$\varphi_{\text{SLM}}^{(m)} = \begin{cases} 0, & \text{if } \Delta I_{\text{holo}}^{(m)} \geq 0 \\ \pi, & \text{if } \Delta I_{\text{holo}}^{(m)} < 0 \end{cases}. \quad (\text{S25})$$

In the playback step, the reference beam is modulated by an SLM with the binary phase map of $\boldsymbol{\varphi}_{\text{SLM}}$. When light passes back through the scattering medium, the light field on the guide star plane is $\mathbf{E}_{\text{OPC}} = A_{\text{R}} \exp(i\varphi_{\text{R}}) \mathbf{T}^T \cdot \exp(i\boldsymbol{\varphi}_{\text{SLM}})$, whose j -th element is

$$\begin{aligned} E_{\text{OPC}}^{(j)} &= A_{\text{R}} \exp(i\varphi_{\text{R}}) \sum_{m=1}^M t_{mj} \exp(i\varphi_{\text{SLM}}^{(m)}) \\ &= A_{\text{R}} \exp(i\varphi_{\text{R}}) \sum_{m=1}^M C_{mj} \exp\left[i\left(\varphi_{mj} + \varphi_{\text{SLM}}^{(m)}\right)\right] \end{aligned} \quad (\text{S26})$$

We assume that $\cos(2\pi f_{\text{mod}} t_0 - \varphi_{\text{b}}) > 0$ in Eq. (S24). From Eqs. (S24–S26), at the position where the guide star resides ($j = 1$), no matter $\varphi_{\text{SLM}}^{(m)} = 0$ or $\varphi_{\text{SLM}}^{(m)} = \pi$, the value $\varphi_{mj} + \varphi_{\text{SLM}}^{(m)}$ distributes uniformly in the range of $[-\pi/2 + \varphi_{\text{R}} - \varphi_0 - \varphi_{\text{add}} + 2k\pi, \pi/2 + \varphi_{\text{R}} - \varphi_0 - \varphi_{\text{add}} + 2k\pi]$ where $k = 1, 2, 3, \dots$. This means photons modulated by different SLM pixels interfere constructively, and thus a bright focus is formed on the guide star. In contrast, at those positions outside the guide star ($j \neq 1$), $\varphi_{mj} + \varphi_{\text{SLM}}^{(m)}$ distributes uniformly within $[0, 2\pi)$, which means that photons interfere randomly, and thus a speckle background is formed.

S4: Simulation parameters of the angular-spectrum modeling

As shown in Fig. S1, the incident laser was a 1-mm diameter collimated beam with a wavelength of 532 nm. The scattering medium has a thickness of 5 mm and a transport mean free path l' of 1 mm. We divided the scattering medium into multiple layers with an interval Δl of 20 μm . For each layer, the mean value of the refractive index was set as $n_{\text{mean}} = 1.4$. The guide star and the fast physiological motion component were set inside the scattering medium with a depth l_1 of 1 mm and a depth l_2 of 3 mm, respectively. The scattered light exiting the scattering medium propagated in free space for a distance d_1 of 30 mm, passed through a collecting lens with a focal length of 40 mm, and finally arrived at the camera plane with a distance d_2 of 80 mm. We discretized the light fields into 1000×1000 points with an interval of 5 μm . The field transmittance through each pixel of the fast physiological motion component randomly varied with an additional phase (uniformly distributed within $[-0.5 \text{ rad}, 0.5 \text{ rad}]$) and an additional amplitude (uniformly distributed within $[-0.03, 0.03]$) at each step. The size of the fast physiological motion component was $0.48 \times 5.00 \text{ mm}^2$, and the time interval was 8.3 ms for each step.

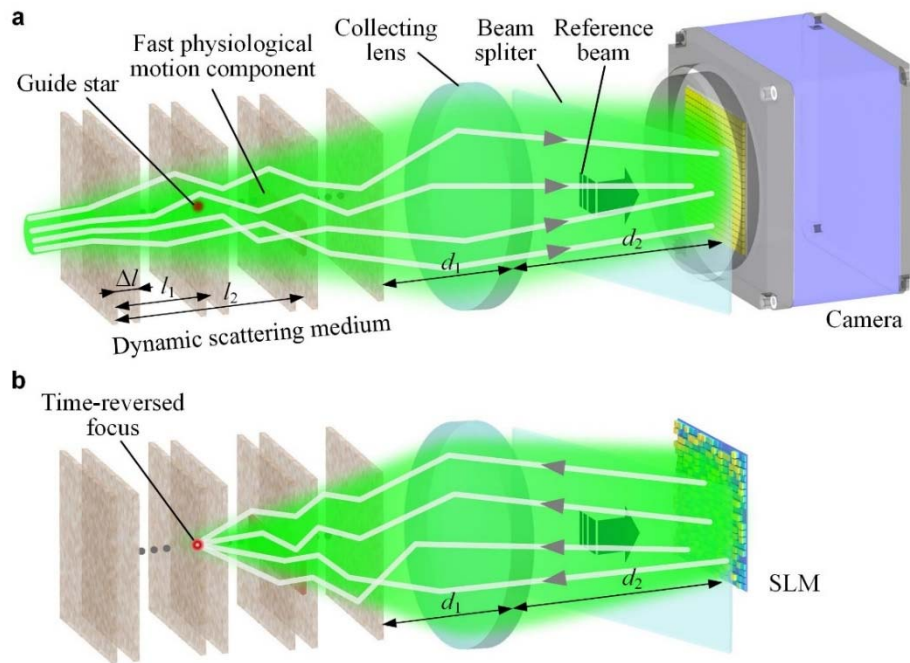


Figure S1. Angular-spectrum modeling of PFM-DOPC. (a) Light propagated through a scattering medium layer by layer with the modulation of the guide star, and holograms formed by the interference of scattered light and reference beam were recorded by a camera. (b) Conjugated-light modulated by an SLM

propagated back layer by layer and focused on the guide star inside the scattering medium.