# Thermal Modeling and Simulation for Optical Illumination to Extract Cancer Cells from Human Tissue Samples

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**Abstract:** Expression microdissection (xMD) allows extraction of target cancer cells from human tissue samples, to reduce misdiagnoses caused by non-target cell contamination. A thermal model and simulations are presented to assess temperature distribution in the xMD process.  **OCIS codes:** (170.3660) Light propagation in tissue; (170.3890) Medical optics instrumentation; (170.6935) Tissue characterization.

## 1. Introduction

Accurate diagnosis of cancer (and other diseases) is hampered by the inability to extract target cells from human biopsy samples. Cancer cells often make up a small fraction of the total number of cells in a biopsy samples. The result is that downstream molecular analyses are confounded by DNA from non-cancer cells, leading to an inability to diagnose (insufficient sample) or worse, misdiagnoses. Expression microdissection (xMD) is an immuno-histo-chemistry (IHC) based method originally developed and patented at NIH [1] that enriches human tissue samples. In this method, the target cells are first stained by a dark IHC stain, a transparent film with a low melting temperature is then placed onto the sample, and then light illumination is passed over the tissue sample. The stains absorb the light, heat up, and melt the film above them, thus binding only the stained target cells (e.g. cancer cells) to the film. When the film is peeled off, the cells attached to it provide a purified patient sample that is almost entirely cancer cells [2-3]. Our goal in this paper is to state and simulate the physics behind the xMD process, so that it can be understood and quantified. Hence we state a thermal model to simulate transient temperature distribution in the xMD media (film, tissue slices, and the underlying glass slides) during laser irradiation.

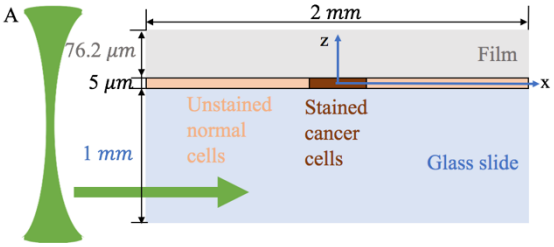
## 2. Methods

We focus on an xMD system which uses a collimated continuous-wave laser to raster the sample. The system geometry is shown in Figure 1A. The transient temperature distribution in the film, tissue, and glass, during laser irradiation can be estimated by solving a heat transfer equation with a moving heat source due to the scanning laser

$$\rho C \frac{\partial T}{\partial t} = \nabla \cdot (k_c \nabla T) + \mu_a \frac{2P_{laser}}{r_0} \exp\left(\frac{-2(x-x_{focus})^2}{r_0^2}\right) \exp(-\mu_a z) \qquad (1)$$

Here $\rho$ is density, $C$ is specific heat, $k_c$ is the thermal conductivity, $\mu_a$ is absorption coefficient, $r_0$ is the radius of laser focal spot, $P_{laser}$ is laser power, and $x_{focus}$ is the position of laser focal spot moving along the x-axis. The boundary conditions include constant room temperature at the bottom of the glass slide and free air convection at the rest of the boundaries. The convection coefficient is 10 $W/(m^2K)$ and ambient temperature is 20℃. Furthermore the following assumptions are used: i) absorption of backscattered light is negligible because both the tissue and film are very thin and have strong forward scattering; ii) optical and thermal properties are thermally stable during the process; iii) radiation emission from the sample is neglected; and iv) there is good thermal contact between the film and the tissue section. COMSOL Multiphysics 5.3 was employed for the solution of heat equation (1).

A




B

| | $\rho$ $(Kg/m^3)$ | $C$ $(J/Kg \cdot K)$ | $K_c$ $(W/m \cdot K)$ | $\mu_a$ $(1/mm)$ |
|---|---|---|---|---|
| Film | 950 | 3140 | 0.335 | 0.24 |
| Tissue | 980 | 3780 | 0.485 | 0.07 |
| Stained tissue | 980 | 3780 | 0.485 | 28 |
| Glass slide | 2230 | 837 | 1.088 | 0 |

Fig. 1. A) Schematic of the media; B) The physical properties used for simulations.

The simulation is performed with the same laser system parameters and a sample configuration that was published in previous studies [2-3]. Specifically, $P_{laser} = 400\ mW$, $r_0 = 100\ \mu m$, the laser scan rate is $v = 3\ cm/s$, and the film melting point is 80℃. No prior study has reported the absorption coefficient of IHC stained tissue, but it is known that absorption can be magnified by the amount of the chromogens depositing on cancer cells. Hence we have selected an estimated absorption magnification factor of 400 based on prior studies [8]. The resulting physical properties of the model are tabulated in Figure 1B [4-8].

For each simulation run, the goal is to quantify how far away in height (z) and in horizontal distance (x) the film has melted away from the edge of the stained cancer cells. Hence Figure 2 shows the results for temperature distribution vertically up in the film (panel A), and horizontally along the film from the edge of the stain (panel B). Then panel C shows the effect due to different laser raster speeds. In panels 2A and 2B, the laser rastering speed is held constant at the previously published value of $v = 3\ cm/s$ and each curve is for a different sized region of stained cancer cells (from 10 $\mu m$ to 300 $\mu m$ diameter). In panel 2A, each curve shows the temperature distribution in the film with height above the tissue, at the time that the laser is centered on the stained region of cancer cells when the maximum temperature occurs. When this temperature exceeds the 80℃ melting point, then the film has melted at this height. Panel 2B shows temperature in terms of horizontal distance from the edge of the stain. If the temperature exceeds the melting point far away from the cancer cells, then the film will be lifting many off-target non-cancer cells (non-specific xMD performance). Hence this plot can be used to assess the spatial accuracy of xMD. Finally, panel 2C examines the effect of the speed of laser rastering. For a cancer region 200 $\mu m$ in diameter, laser speed was varied from 1 to 3 $cm/s$ and again temperature was recorded along the horizontal axis to assess xMD spatial resolution.

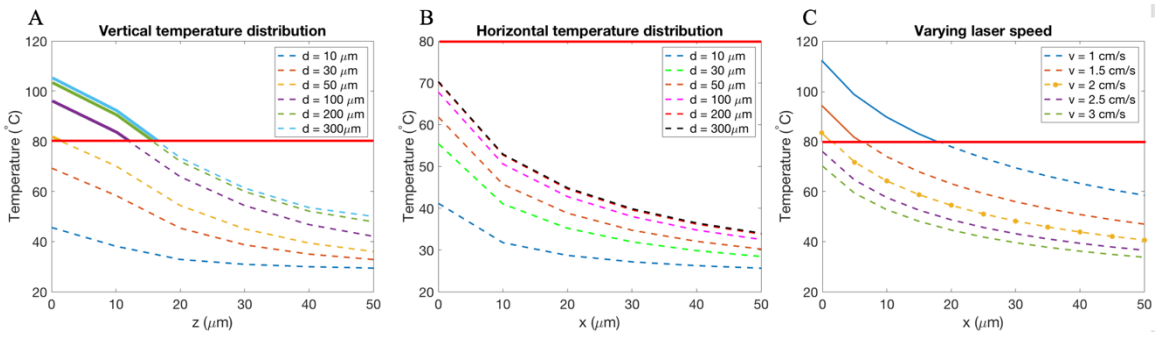



Fig. 2. Temperature along A) the z axis and B) x axis. C) Temperature along the x axis for different laser speeds.

## 3. Conclusion

Above simulations were used to better understand the xMD process. At the previously published laser rastering speed of $v = 3\ cm/s$, they indicated that the region of the film melted did not adequately cover the cancer cells for all cancer region sizes examined. This means that xMD is not lifting as many cancer cells as it could lift. Hence we examined decreasing the laser rastering speed (Figure 2C). The simulations indicated that a speed of 2 $cm/s$ gives a good balance between efficiency (lifting as many cancer cells as possible) and specificity (not lifting non-cancer cells). When the laser speed was 2 $cm/s$, then the temperature was above melting at the edge of the cancer cells, at $x = 0$ (marked by the starred point on the orange star curve), but then decreased to below melting by $x \approx 2\ \mu m$. Hence the simulation can be used to understand how to select laser rastering speeds to balance high efficiency (get all the cancer cells) versus good specificity (do not lift non-cancer cells, do not melt the film above off-target cells).

## 4. References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