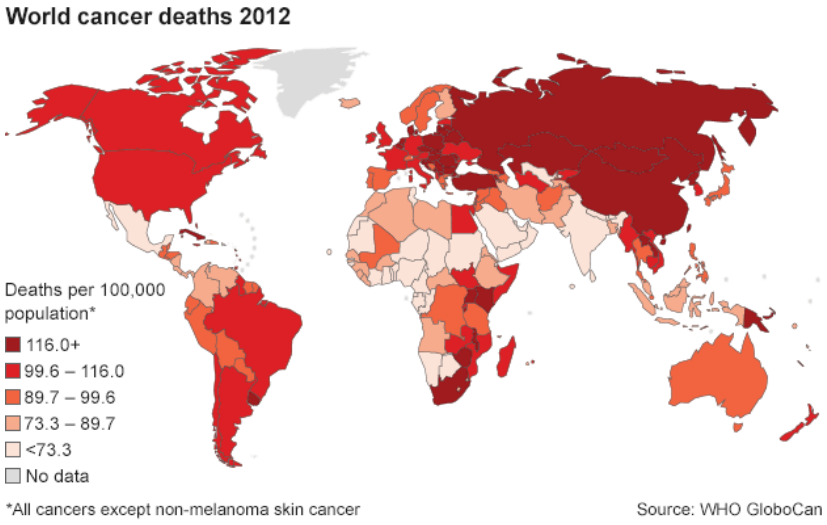
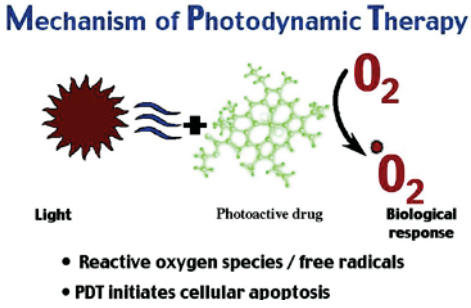
As is well-documented, cancer is a leading cause of death world-wide. In 2009 in the US alone $86,600,000,000 was spent on cancer treatment with 1.7 million new cases and 0.6 million deaths. Worldwide the numbers are 14 million and 8.2 million, respectively. The number of cancer deaths is only increasing. Current treatments include surgery, chemotherapy and radiation therapy. Yet each of these treatments has disadvantages such as long treatment times and damage to normal tissue.



Light treatment is an effective alternative to current cancer treatments

While the general treatment has been known for some time, a different modality is emerging, namely, photodynamic therapy (PDT) that involves light, light drug (photosensitizer, PS) and oxygen. In PDT, light drug is injected into the body before treatment begins and accumulates at higher concentrations in diseased tissue compared to normal tissue.

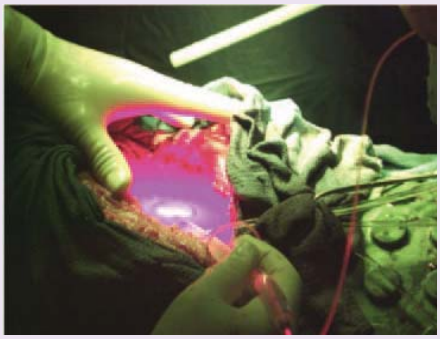
Diagram of Light, Photoactive light drug and molecular oxygen



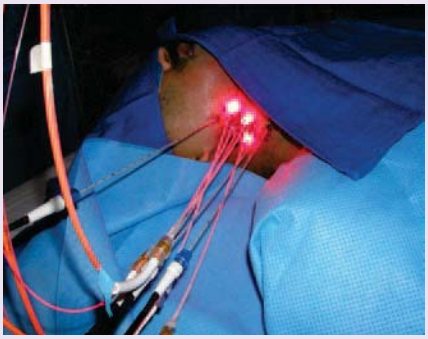
Laser light is introduced into the tumor via optical fibers. The light drug absorbs the light and transfers its energy to surrounding molecular oxygen, which in turn becomes a highly reactive ion known as singlet oxygen. Unlike chemotherapy, PDT does not cause systemic toxicities, and unlike radiation therapy it does not cause cumulative

damage in the local field. It should be noted that PDT is used in many applications, such as oral cavity disease, blood products purification, cardiovascular diseases, autoimmune diseases, bacterial infections, eye and skin diseases. The ability of PDT to spare surrounding critical normal structures and better healing after treatment distinguish the benefit of PDT compared to other localized therapeutic approaches, such as surgical excision or tissue X-ray radiation.

These pictures show PDT treatments in human lung in the operating room (OR) at the Hospital of the University of Pennsylvania (Penn) and head and neck in the OR at Roswell Park Cancer Institute (RPCI), respectively. Simphotek is partnering with both Penn and RPCI.



PDT treatment in human lungs



Head and neck PDT treatment

In search for effective PDT treatment planning system

While PDT has demonstrated strong clinical efficacy data in many cases, PDT treatment planning remains rudimentary for most clinical applications. Inadequate treatment planning can lead to increased rates of under- or over-treatment that manifest clinically as local recurrence or local toxicity. Certain components of treatment planning exist such as CT scanning for geometry, but critical component(s) needed to make PDT treatment planning effective in the clinic are lacking. These components include: (1) Monte Carlo (MC) light intensity calculations that should be done in minute(s) in the treatment clinic so the physician can adjust the laser power for various regions of the tumor and (2) real time photokinetic calculations to determine the cytotoxic effects of the PS depending on its concentration and distribution within a tumor. Compared to the sophisticated computational planning tools that are available for ionizing radiation therapy most PDT computational planning tools are relatively simplistic and not effective for achieving personalized treatments.

Monitor and optimize PDT with SimphoSOFT

Improvements for PDT efficacy can be achieved by accurate modeling all the photokinetic processes involved in PDT. Our simulation software SimphoSOFT provides a high accuracy in modeling PDT by considering the most complete to this date mathematical model which describes interaction of light, PS drug, oxygen and target cancer cells.

Light drug photokinetics equations

$$\partial\left[S_0\right]/\partial\tau = -(\varepsilon\varphi/h\upsilon_0)\left[S_0\right] - \mathrm{k}_1\left[{}^1O_2\right]\left[S_0'\right] + \mathrm{k}_2[T]\left[{}^3O_2\right] + \mathrm{k}_3\left[S_1\right] + \mathrm{k}_4[T]$$

$$\partial\left[S_1\right]/\partial\tau = -\left(\mathbf{k_3} + \mathbf{k_5}\right)\left[S_1\right] + \mathbf{k_0}\left[S_0\right]$$

$$\partial[T]/\partial\tau = -\mathbf{k_2}[T]\left[{}^3O_2\right] - \mathbf{k_4}[T] + \mathbf{k_5}\left[S_1\right]$$

$$\partial\left[{}^3O_2\right]/\partial\tau = -0.5\mathbf{k_2}[T]\left[{}^3O_2\right] + \mathbf{k_6}\left[{}^1O_2\right] + 0.7\left(1 - \left[\left[{}^3O_2\right]/\left[{}^3O_2\right]t = 0\right]\right)$$

$$\partial\left[{}^1O_2\right]/\partial\tau = -\mathbf{k_1}\left[{}^1O_2\right]\left[S_0'\right] + 0.5\mathbf{k_2}[T]\left[{}^3O_2\right] - \mathbf{k_6}\left[{}^1O_2\right] - \mathbf{k_7}[A]\left[{}^1O_2\right]$$

$$\partial[A]/\partial\tau = -\mathbf{k_7}[A]\left[{}^1O_2\right]$$

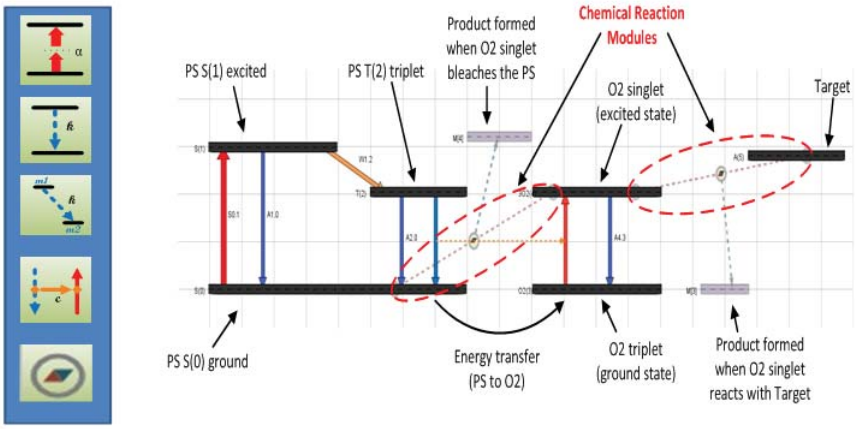
These equations are given in simplified matrix form by

$$\frac{\partial\mathbf{N}(\tau)}{\partial\tau} = \left[d_0\mathbf{D}_0 + d_0\mathbf{D}_{\text{egy}} + d_0\mathbf{D}_{CR} + \sum_{\alpha=1}^{N_A} d_\alpha\mathbf{D}_\alpha\varphi^\alpha\right]\mathbf{N}(\tau)$$

where $\mathbf{D}_0$ is a constant $S\times S$ matrix of decay rates $k_{s_2s_1}$, $\mathbf{D}_\alpha$ is a matrix for extinction coefficients $\varepsilon_{s_1s_2}^{[\alpha]PA}$ when α photons are absorbed, $\mathbf{D}_{\text{egy}}$ is an energy transfer matrix containing c_{da} linking the donor and acceptor energy levels, $\mathbf{D}_{CR}$ is a matrix containing $t_{m_1m_2}$ linking components in a chemical reaction (e.g. photobleaching), d_0, d_α are constants. The vector $\mathbf{N}(\tau)$ contains the time dependent concentrations of the ground, first excited singlet and triplet PS concentrations, and the ground triplet and excited singlet state oxygen concentrations. In Fig. 3 the concentrations of the ground state, excited state, triplet state of the PS, molecular oxygen, singlet oxygen and the target are given by $\left[S_0\right]$, $\left[S_1\right]$, $[T]$, $\left[{}^3O_2\right]$, $\left[{}^1O_2\right]$, $[A]$, respectively. The Simphotek patented APBB algorithm is used to solve the photokinetic equations.

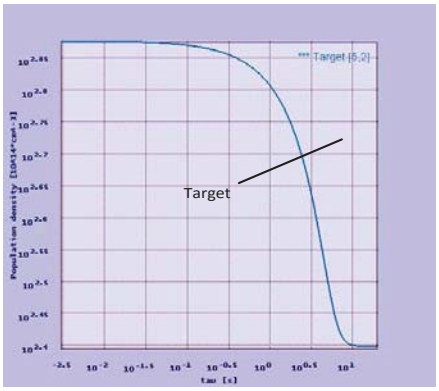
Simphotek's algorithm is unique in its ability to enable users to calculate photokinetics of potentially all different types of light drugs by setting up and calculating the series of interconnected partial differential equations needed to simulate PS photophysics using icons from the screen rather than writing or modifying software code directly, which is required by all other programs. This work sets a new paradigm for dosimetry in PDT as it involves both the light transport variability and the PS variability among different patients and different types of PSs.

Screenshot of SimphoSOFT panel with energy level diagram used for calculations.
The icons on the left represent photon absorption, electron relaxation, energy transfer and chemical reactions/photo bleaching, respectively



SimphoSOFT predicts singlet oxygen concentration – the main ingredient in killing cancers cells – for the entire PDT session as a function of time. Yet this simulation assumes a plane wave. Details of this calculation are given in our PDT case study.

SimphoSOFT singlet oxygen calculations



Simphotek is also partnering with Tech-X Corporation to incorporate their MC calculations with its photokinetic calculations. Our collaborations may produce the first computational method for creating a usable treatment planning system for cancer using PDT.

211 Warren Street, Newark, NJ 07103 info@simphotek.com (973) 621-2340
www.simphotek.com

simphotek
Light Interactions Matter