Supplemental data for Online Only

Supporting Information

To save space of the equations, we introduce the following notations: $L, L_1, P, A, A_r, S, L_r,$ and L_a representing the concentration of lipid, lipid peroxyl radical, lipid peroxide, vitamin E, vitamin E radical, hydroxyl radical, lipid radical, and lipid alkoxyl radical.

Non-dimensionalization

The free radicals with unpaired electrons are transient products during the chemical reactions shown in Table 1, and the concentrations of L_1, L_r, L_a, S, and A_r are extremely small. The typical scale of L_1 is 10^{-6} M (42). The tropospheric hydroxyl radical concentration is in the order of 10^{-15} M. An adult of 70kg body weight inhales oxygen at a rate of 14.7 mol/day. Assuming that 1% converts to free radicals, then the total production rate of ROS, k_s, can be calculated by 14.7/24/70 × 0.01 mol/(L· h) = 8.75 × 10^{-5} M/h (6). Since the half life of the hydroxyl radical is approximately 2.4 × 10^{-10} s (36) (Table 5), we can also estimate the concentration S to be in the range of $8.75\times10^{-5}\times2.4\times10^{-10}/(3600\times\ln\ 2)$ to 10^{-17} M. Based on the above we expect S to be in the magnitude of 10^{-15} to 10^{-17} M. We further assume, based on (36), that L_r, L_a are of the order 10^{-10} M and that A_r is of the order 10^{-6} M.

In view of the above estimates, we non-dimensionalize the system by setting the typical length scale l_0 to be 1cm, time scale to be 1 hour, and scaling the parameters and chemical concentrations as follows:

$$L_{10} = 10^{-6} M,\ L_{r0} = 10^{-10} M,\ L_{a0} = 10^{-10} M,\ A_{r0} = 10^{-6} M,\ S_0 = 10^{-15} M.$$

The non-dimensionalized parameters are defined by:

$$\{L', P'\} = \frac{1}{L_0}\{L, P\},\ A' = \frac{A}{A_0},\ A_r' = \frac{A_r}{A_{r0}},\ L_1' = \frac{L_1}{L_{10}},\ L_r' = \frac{L_r}{L_{r0}},\ L_a' = \frac{L_a}{L_{a0}},\ S' = \frac{S}{S_0},$$

$$\{D_P', D_A', D_{A_r}', D_{L_1}', D_{L_r}', D_{L_a}', D_S'\} = \frac{t_0}{l_0^2}\{D_P, D_A, D_{A_r}, D_{L_1}, D_{L_r}, D_{L_a}, D_S\},$$

$$\{k_{a1}', k_{a2}'\} = \frac{t_0}{A_0}\{k_{a1}, k_{a2}\}, \{k_3', k_6', k_7', k_8', \mu_a', \mu_s'\} = t_0\{k_3, k_6, k_7, k_8, \mu_a, \mu_s\},$$

$$\{\lambda_2', \lambda_4', \lambda_5', \lambda_9', \lambda_{10}'\} = t_0\{\lambda_2 S_0, \lambda_4 L_{10}, \lambda_5 L_{a0}, \lambda_9 L_{10}, \lambda_{10} L_{r0}\},$$

$$\{\lambda_{11}', \lambda_{12}', \lambda_{13}', \lambda_{14}', \lambda_{15}'\} = t_0\{\lambda_{11} L_{a0}, \lambda_{12} L_{r0}, \lambda_{13} L_{10}, \lambda_{14} L_{10}, \lambda_{15} A_{r0}\}.$$

Dropping the primes, for simplicity, the non-dimensionalized system of Eqs. (1-8) takes the following form:

$$\frac{\partial L}{\partial t} = -\underbrace{\lambda_2}_{1.8\times10^{-3}} SL - \underbrace{\lambda_4}_{6.84\times10^{-2}} L_1 L - \underbrace{\lambda_5}_{3.6} L_a L,$$

$$\frac{\partial L_1}{\partial t} = D_{L_1}\nabla^2 L_1 + \underbrace{\frac{k_3 L_{r0}}{L_{10}}}_{1.08\times10^4} L_r + \underbrace{\frac{k_7 L_0}{L_{10}}}_{1.8\times10^4} P - \underbrace{\frac{\lambda_4 L_0}{L_{10}}}_{1.71\times10^3} LL_1 - 2\underbrace{\lambda_9}_{2.376\times10^2} (L_1)^2$$

$$- \underbrace{\lambda_{12}}_{3.6\times10^{-2}} L_r L_1 - \underbrace{\frac{\lambda_{13} A_0}{L_{10}}}_{1.44\times10^6} AL_1 - \underbrace{\frac{\lambda_{14} A_{r0}}{L_{10}}}_{72} A_r L_1,$$

$$\frac{\partial P}{\partial t} = D_P \nabla^2 P + \underbrace{\lambda_4}_{6.84\times10^{-2}} L_1 L + \underbrace{\frac{\lambda_{13} A_0}{P_0}}_{57.6} AL_1 - \underbrace{(k_6 + k_7 + k_8)}_{0.54+0.72+0.027} P,$$

$$\frac{\partial A}{\partial t} = D_A \nabla^2 A + \underbrace{k_{a1}}_{0.35} + \underbrace{k_{a2}}_{\text{treatment}} - \underbrace{\lambda_{13}}_{3.6\times10^3} AL_1 - \underbrace{\mu_a}_{0.35} A,$$

$$\frac{\partial A_r}{\partial t} = D_{A_r}\nabla^2 A_r + \underbrace{\frac{\lambda_{13} A_0}{A_{r0}}}_{1.44\times10^6} AL_1 - \underbrace{\lambda_{14}}_{72} A_r L_1 - \underbrace{2\lambda_{15}}_{4.752\times10^2} A_r^2,$$

$$\frac{\partial S}{\partial t} = D_S \nabla^2 S + \underbrace{\frac{k_8 L_0}{S_0}}_{6.75\times10^{11}} P - \underbrace{\frac{\lambda_2 L_0}{S_0}}_{4.5\times10^{10}} SL - \underbrace{\mu_s}_{1.313\times10^3} S,$$

$$\frac{\partial L_r}{\partial t} = D_{L_r}\nabla^2 L_r + \underbrace{\frac{\lambda_2 L_0}{L_{r0}}}_{4.5\times10^5} SL + \underbrace{\frac{\lambda_4 L_0}{L_{r0}}}_{1.71\times10^7} L_1 L + \underbrace{\frac{\lambda_5 L_0}{L_{r0}}}_{9\times10^6} L_a L$$

$$- \underbrace{k_3}_{1.08\times10^8} L_r - \underbrace{2\lambda_{10}}_{4.752\times10^{-2}} L_r^2 - \underbrace{\frac{\lambda_{12} L_{10}}{L_{r0}}}_{360} L_r L_1,$$

$$\frac{\partial L_a}{\partial t} = D_{L_a}\nabla^2 L_a + \underbrace{\frac{(k_6 + k_8) L_0}{L_{a0}}}_{1.4175\times10^8} P - \underbrace{\frac{\lambda_5 L_0}{L_{a0}}}_{9\times10^6} L_a L - \underbrace{2\lambda_{11}}_{4.752\times10^{-2}} L_a^2.$$

The simplified model

From the non-dimensionalized equations, we see that in the equations for $L_1, A_r, S, L_r,$ and L_a, the chemical reactions are very fast (on a time scale of fraction of seconds), and the linear and quadratic decay terms have very large coefficients. Therefore we may assume the quasi-steady state of $L_1, A_r, S, L_r,$ and L_a. We then obtain the following simplified model,

$$\frac{\partial L}{\partial t} = -\lambda_2 SL - \lambda_4 L_1 L - \lambda_5 L_a L, \tag{10}$$

$$\frac{\partial P}{\partial t} = D_P \nabla^2 P + \lambda_4 L_1 L + \lambda_{13} A L_1 - (k_6 + k_7 + k_8)P, \tag{11}$$

$$\frac{\partial A}{\partial t} = D_A \nabla^2 A + k_{a1} + k_{a2} - ld_{13} A L_1 - \mu_a A, \tag{12}$$

$$0 = \lambda_{13} A L_1 - \lambda_{14} A_r L_1 - 2\lambda_{15} A_r^2, \tag{13}$$

$$0 = k_3 L_r + k_7 P - \lambda_4 L L_1 - 2\lambda_9 (L_1)^2 - \lambda_{12} L_r L_1 - \lambda_{13} A L_1 - \lambda_{14} A_r L_1, \tag{14}$$

$$0 = k_8 P - \lambda_2 SL - \mu_s S, \tag{15}$$

$$0 = \lambda_2 SL + \lambda_4 L_1 L + \lambda_5 L_a L - k_3 L_r - 2\lambda_{10} L_r^2 - \lambda_{12} L_r L_1, \tag{16}$$

$$0 = (k_6 + k_8)P - \lambda_5 L_a L - 2\lambda_{11} L_a^2, \tag{17}$$

together with the boundary conditions on the computational domain,

$$L = L_0,\ P = 0,\ A = A_0 \quad \text{on the bottom and side faces,}$$

$$\frac{\partial L}{\partial z} = \frac{\partial P}{\partial z} = \frac{\partial A}{\partial z} = 0 \quad \text{on the top face,}$$

and the initial conditions

$$L = L_0,\ P = 0,\ A_0 = k_{a1} / \mu_a \quad \text{outside the initial wound}$$

$$L = A = 0,\ P > L_0 / 2 \quad \text{inside the initial wound}$$

Eqs. (10)-(12) are solved by using semi-implicit scheme. In 3-D the scheme is

$$\frac{L^{(k+1)} - L^{(k)}}{dt} = -\lambda_2 S^{(k)} L^{(k+1)} - \lambda_4 L_1^{(k)} L^{(k+1)} - \lambda_5 L_a^{(k)} L^{(k+1)},$$

$$\frac{P^{(k+1)} - P^{(k)}}{dt} = D_P \Delta_6 P^{(k)} + \lambda_4 L_1^{(k)} L^{(k)} + \lambda_{13} A^{(k)} L_1^{(k)} - (k_6 + k_7 + k_8) P^{(k+1)},$$

$$\frac{A^{(k+1)} - A^{(k)}}{dt} = D_A \Delta_6 A^{(k)} + k_{a1} + k_{a2} - ld_{13} A^{(k+1)} L_1^{(k)} - \mu_a A^{(k+1)},$$

where Δ_6 is the standard 6 points central discretization of the Laplace Operator. In this discretization, the variables stay non-negative. Solving next Eqs. (15)-(17), we obtain

$$S^{(k+1)} = \frac{k_8 P^{(k+1)}}{\lambda_2 L^{(k+1)} + \mu_s}, \quad L_a^{(k+1)} = \frac{2(k_6 + k_8) P^{(k+1)}}{\lambda_5 L^{(k+1)} + \sqrt{(\lambda_5 L^{(k+1)})^2 + 8\lambda_{11}(k_6 + k_8) P^{(k+1)}}}.$$

Notice that Eqs. (13), (14), and (16) are quadratic equations for $A_r, L_1,$ and L_r respectively. There are no simple closed form solutions. We compute the stationary solution by iterating $A_r, L_1,$ and L_r in terms of other variables, using quadratic formulas until the tolerance of solutions between two successive iterations is below 10^{-12}. For example, the quadratic equation for A_r is

$$c_2 A_r^2 + c_1 A_r + c_0 = 0,$$

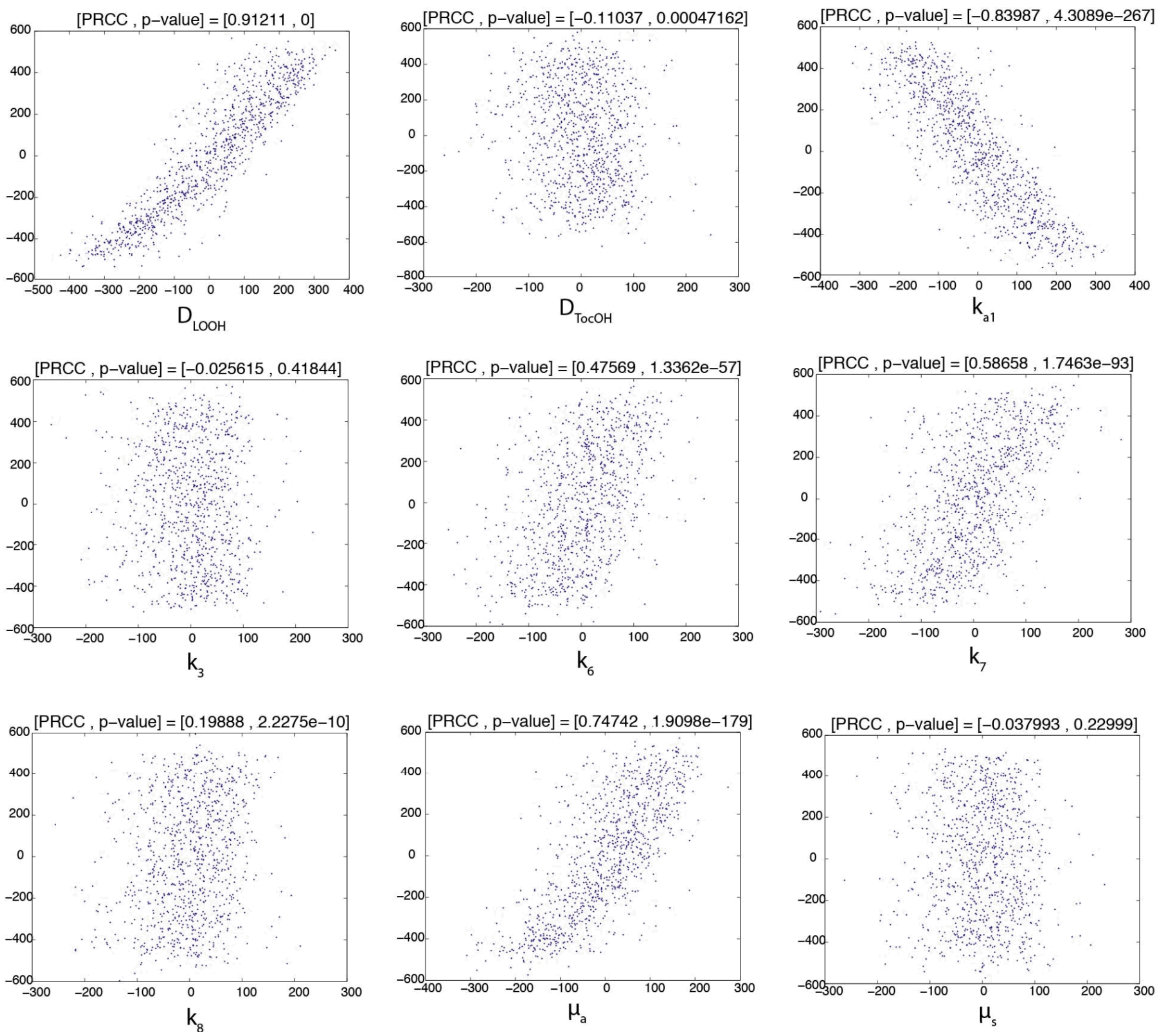
where $c_2 = 2\lambda_1$, $c_1 = \lambda_4 L_1$, and $c_0 = -\lambda_3 A L_1$. We choose

$$A_r = \frac{-c_1 + \sqrt{c_1^2 - 4c_2 c_0}}{2c_2}$$

to ensure that the stationary solution is positive.

We solved the full model and the simplified model using central difference for the spatial discretization of diffusion and second-order backward differentiation formulas for the resulting ODE system. We found that the numerical results for the two models are virtually indistinguishable under the parameters of our model in a one-dimensional geometry with no-flux boundary conditions and under various biologically reasonable initial conditions (not shown here). Thus the quasi-steady state simplification is justified numerically.

Sensitivity analysis



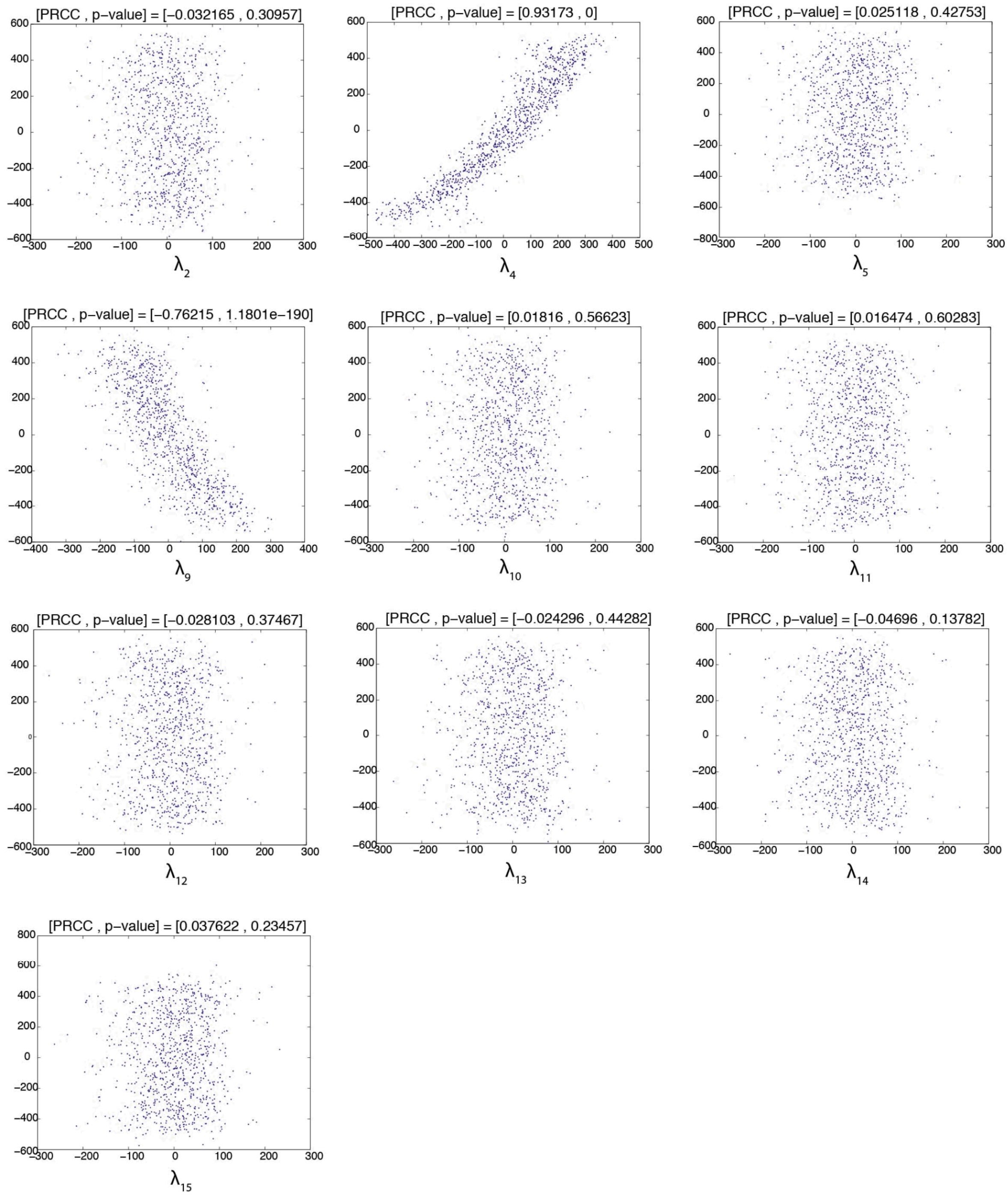


Figure S1. PRCC sensitivity analysis for the burn propagation at $T = 12$ in two-dimensional simulations on 19 parameters. PRCC values and p-values for these 19 parameters are listed on the top of each subfigure. We found that the following parameters D_{LOOH}, μ_a, λ_4 are highly positively correlated while the parameters k_{a1}, λ_9 are highly negatively correlated.