Mathematical Model of Heat Damage of Cells

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Motivation

MATH 454 Take-home Exam:

How long can a person hold a coffee stirrer?

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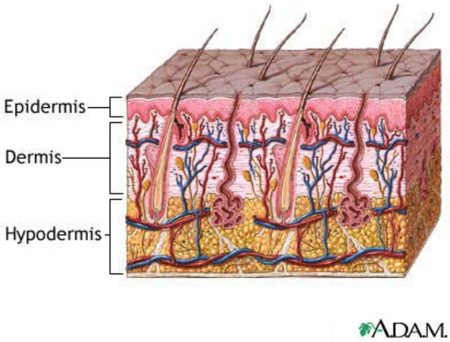
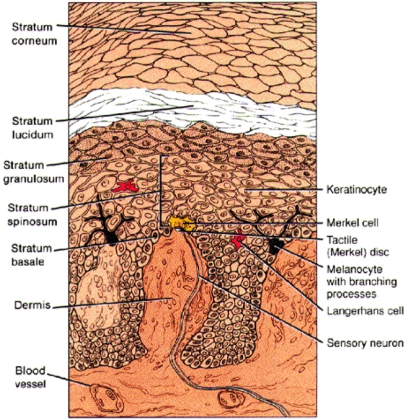
Motivation

Burn injuries are a typical case of heat damage to living cells:

Skin Anatomy





Degree of Burn [Diller]

First Degree Burns

- Moderate vasodilatation, increased permeability of endothelium, reddening of the tissue.

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Second Degree Burns

- Capillary damage;
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Third Degree Burns

- Burn of all epidermal elements;
- Local blood vessels obliterated.

Epidermal Wound Healing, Heat Damage of Cells

Epidermal Wound Healing [Murray]

- Diffusion of living cells into dead regions;
- Mitotic generation of new cells;
- First order kinetic, traveling waves.

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Thermal Damage of Cells [Henriques]

- Thermal denaturation (unfolding) of enzymes;
- Alternations in cell metabolic processes;
- Nonprotein alternations in cells as changes in ion concentrations, break up of lipid membrane, etc.

Key Factors in Burn Injury

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- Thermal denaturation (unfolding) of enzymes;
- Increased vascular permeability;
- Heat flow in the non-homogeneous skin environment.

Experimental Data [Henriques & Mortiz]

Standard hypertermia reference data

- Multiple skin burns of human and porcine skin $(44^\circ, 100^\circ)$;
- Single and repeated exposures of a fixed time;
- Dermal reactions categorized after a certain time;
- Duplicate exposures in borderline cases.

Experimental Data [Henriques & Mortiz]

Major observations

- Very small quantitative difference in the susceptibility of human and porcine epidermis to thermal injury;
- Optimal thermal milieu of the epidermal cells lies within a few degrees of normal physiological temperature;
- Two phases: heat saturation (temperature growth), stable temperature gradient;
- Repeated exposure does not cumulate in a simple way, recovery period influences damage;
- Pressure does not significantly influence thermal injury.

Further Literature

- Medicine (Thermal wounds, treatment, healing; hyperthermal cancer treatment; skin aging);
- Biomechanics and biomedical engineering (Details of thermal injury process, heat-shock response, vascular permeability);
- Fire protection (Comparison of different fire protecting materials);
- Mathematical biology (Numerical solutions to heat flow in human skin coupled to vascular flow, different means of heat transport);
- Biochemistry (Alternations of metabolic processes, glycolysis);
- Biomedical Optics (Thermometry methods).

Moritz and Henriques: Damage Function

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A first order chemical reaction process – the Arrhenius equation:

$$\frac{d\Omega}{dt} = Ae^{-G/RT} .$$

- $\Omega(t)$ – a damage function;
- G – an activation energy for the reaction;
- $T(t)$ – absolute temperature of a local tissue (calculated from the heat equation at the basal layer).

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The total thermal damage over the time interval t_0, t_1

$$\Omega = \int_{t_0}^{t_1} Ae^{-G/RT(t)} dt .$$

Xu and Qian: Improved Model

Based on Michaelis-Menten kinetics and transition state theory:

$$E + S \underset{k^-}{\overset{k^+}{\rightleftharpoons}} ES \xrightarrow{k} E + P, \qquad E \xrightarrow{k_d} E_u$$

- E – concentration of an enzyme;
- S – concentration of a substrate;
- ES – concentration of a complex;
- P – concentration of a product;
- E_u – concentration of an unfolded enzyme.

Xu and Qian: Improved Model

$$E + S \underset{k^-}{\overset{k^+}{\rightleftharpoons}} ES \xrightarrow{k} E + P$$

$$E \xrightarrow{k_d} E_u$$

Xu and Qian: Improved Model

$$
\begin{array}{ccccc}
E + S & \underset{k^-}{\overset{k^+}{\rightleftharpoons}} & ES & \xrightarrow{k} & E + P \\
\downarrow k_d & & & & \\
E_u & & & &
\end{array}
$$

Assumptions

- $k_d << k$;
- $k_- << k$;
- only free form of the enzyme is deactivated;
- the substrate concentration S constant during the process.

Xu and Qian: Improved Model

Transition state theory:

$$k_d = k_{d0} \exp\left(-\frac{G_d}{RT} + \frac{G_d}{RT_0}\right) = r_0 e^{\alpha\theta}\,.$$

Parameters:

- $\alpha = G_d R T_0$;
- $\theta = (T - T_0)/T_0$;
- $\beta = (G - G^{+})/RT_0$.

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Transition state theory:

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- $\theta = (T - T_0)/T_0$;
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Then using Quasi-Steady State approximation

$$\Omega = \int_{t_0}^{t_1} \frac{Ae^{\alpha\theta}}{1 + Be^{-\beta\theta}} dt .$$

Xu and Qian: Criticism

Biological Reasons

- Only a single cell damage, parameter matching without the heat equation.
- Unlimited damage for any temperature.
- Bad match for large temperatures.
- Does not match repeated exposure experiments.

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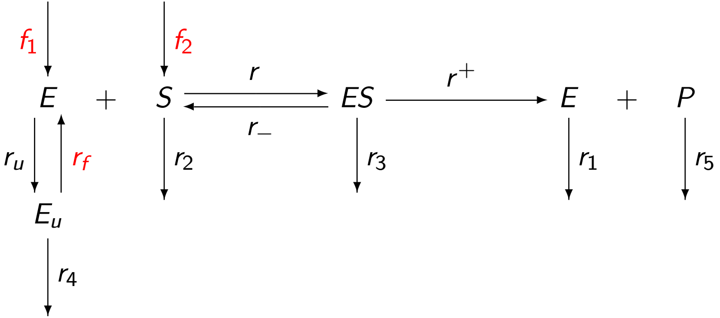
Mathematical Reasons

- Without sources, the system goes to equilibrium.
- Quasi-steady state not reached in numerical simulations.

Assumptions

- Unfolding and refolding of enzymes;
- Zero state (dead cell) is a stable equilibrium;
- At a physiological level there is a nontrivial stable equilibrium;
- Sources of enzyme and substrate depend on the state of the system;
- Sources of the substrate are due to cell exterior with saturation;
- 1 Neglect the effect of increased permeability of blood vessels.

Proposed Improved Model for a Single Cell



Equilibria of the Proposed Improved Model

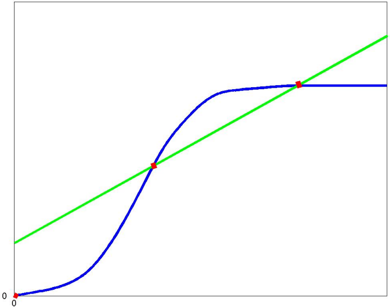


Figure: Two intercepts correspond to two equilibria of the system, the trivial state is an equilibrium as well.

Equilibria of the Proposed Improved Model

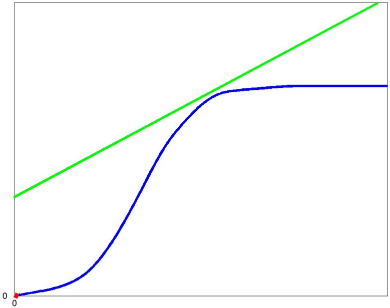
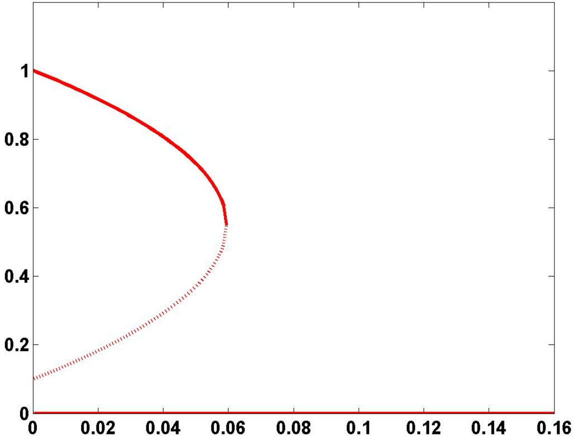


Figure: Under a reasonable assumption on activation energies the curves do not intersect for a larger temperature and the two equilibria will disappear via a saddle-node bifurcation. A ghost of equilibria appears close to the trivial state.

Simplified Saddle-Node Bifurcation Model



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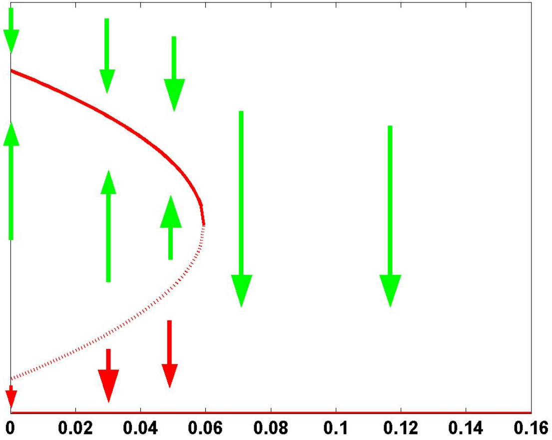

Simplified Saddle-Node Bifurcation Model

Important Features

- The attractive trivial state for all temperatures (dead cell), exponential rate very close to zero;
- At temperatures close to physiological temperature stable non-trivial equilibrium;
- At temperatures very close to normal physiological temperature, the system is able to adjust, particularly thermal cell death does not happen.
- A ghost of equilibria (critical slow-down) closer and closer to zero with an increasing temperature;
- Possible hysteresis effect that explains repeated exposure data;

Simplified Saddle-Node Bifurcation Model

Additional Assumptions

- Biochemical processes in the cell are governed by the transition state theory.
- The system is governed by three principal rates:
  - the typical rate of the main chemical reaction,
  - the typical rate of deactivation/degradation/melting of various chemicals,
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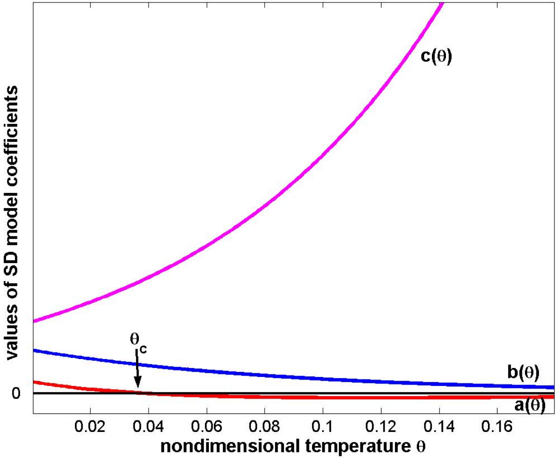
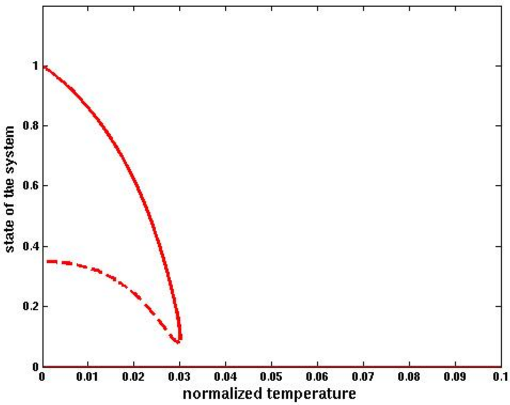
Saddle-Node Bifurcation Model

$$\frac{dy}{dt} = f(y) = -cy\left((y-b)^2 - a\right) .$$

Coefficients of the Saddle-Node Model



Saddle-Node Bifurcation Model Including Transition State Theory



Real Setting

- Heat conduction modeled by a 3D heat equation;
- Heat is also convected by fluid in blood vessels;
- A Newton boundary condition outside;
- Nonhomogeneous environment changing with the burn injury;
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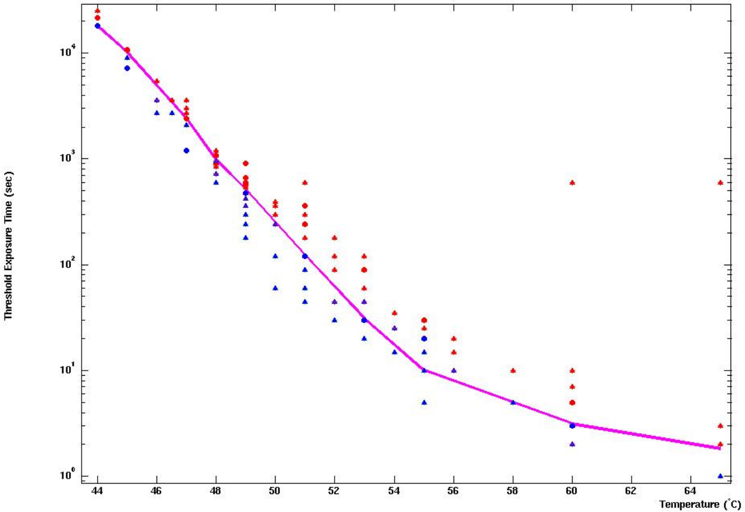
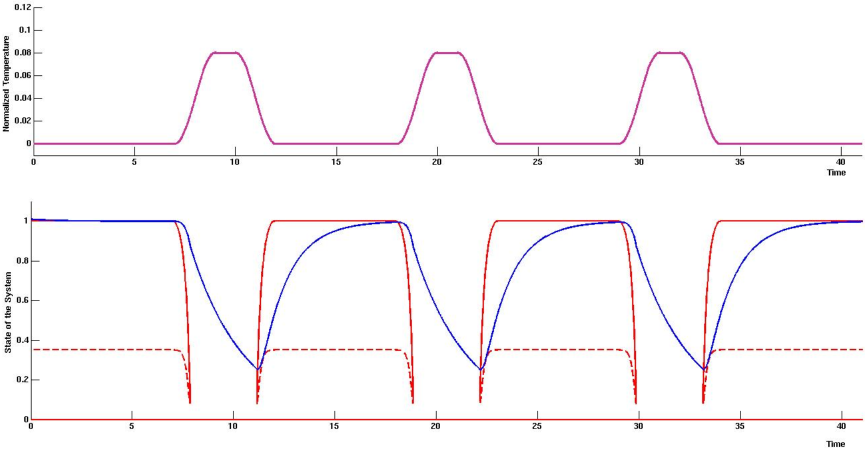
Simple Mathematical Model

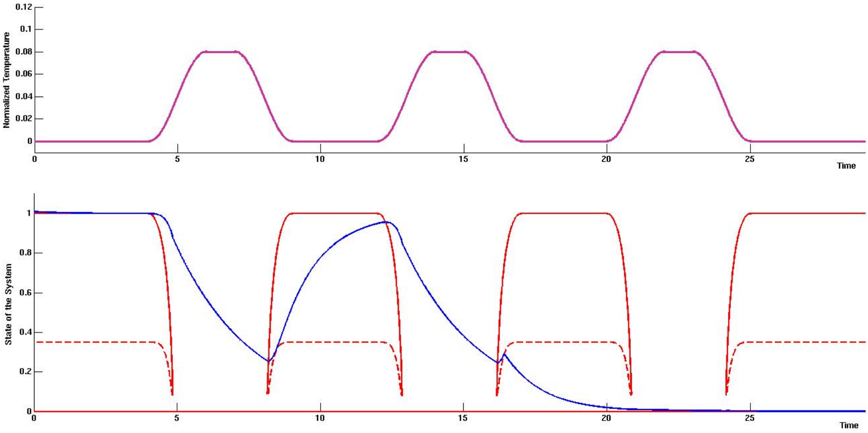
- Heat conduction modeled by a 1D heat equation;
- Constant temperature boundary condition outside;
- Homogeneous environment;
- A homogeneous Neumann boundary condition $(dT/dz = 0)$ at the inner side.


Threshold Exposure Time (sec)
Temperature (°C)
10^4
10^3
10^2
10^1
10^0
44
46
48
50
52
54
56
58
60
62
64

Repeated Exposure Results I



Repeated Exposure Results II



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- We considered a general chemical kinetics model with sources and proved that the system undergoes a saddle-node bifurcation at some critical temperature slighly above the normal physiological conditions.
- We suggested a simple phenomenological model for the saddle-node bifurcation.
- We matched the available parameters to results of biomedical experiments.

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- Consider (or derive) a more realistic boundary condition at the point of contact with the hot object.

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- Include more realistic model for the heat flow, non-homogeneous heat equation in 2D and 3D.
- Capture the role of the shape of the basal layer for prevention against burn injuries.
- Add radiation and convection to the heat flow;
- Consider (or derive) a more realistic boundary condition at the point of contact with the hot object.
- Experimentally test the prediction for small and large temperatures.


CAUTION
HOT SURFACE
DO NOT
TOUCH