Multiphysics Modeling of Ambient Gas Plasma-Based Wound Healing Process

Yuki Sakiyama, Marat Orazov, and David Graves

Department of Chemical and Biomolecular Engineering
University of California at Berkeley
Outline

1. Introduction
   • overview of gas plasma-based wound healing
   • importance of ROS/RNS
   • our strategy

2. Modeling of Surface DBD
   • model description
   • plasma-generated ROS/RNS

3. Modeling of wound healing
   • model description
   • possible effects from gas plasma

4. Concluding remarks
Introduction: wound healing process

Inflammatory phase
- ~48 hours
- bacteria sterilization/debris removal
- blood coagulation

Proliferative phase
- 2~10 days
- blood vessels generation
- collagen deposition from fibroblasts

Remodeling phase
- 1 year
- tissue reorganization/realignment
- apoptosis of unnecessary cells
Introduction: known effects of gas plasmas

R. A. Bryant, et al., *Acute and Chronic Wounds* (Mosby, Missouri, 2006).

Inflammatory phase
- ~48 hours
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Remodeling phase
- 1 year
- tissue reorganization/realignment
- apoptosis of unnecessary cells
Introduction: ongoing projects

• Plasma health care project
• lead by G. Morfill at Max-Planck Institute
• 19 PhDs, 11 MDs
• Germany, UK, Russia, Japan, USA

Phase-I clinical study


Microwave Ar plasma torch

Before treatment  After 11 treatments
Introduction: modeling strategy


- Power density: 0.1-1.0 W/cm²
- Voltage: 10-20 kV_{pkpk}
- Frequency: 1-10 kHz

**Mechano-chemical model of cell/tissue/system**

Plasma dynamics/chemistry
Mass transportation

Plasma-biomaterial interaction

Wounded tissue
Healthy tissue
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SDBD: model description (1)

For charged particles:
\[ \Gamma_{pg} = 0 \]

For neutrals:
\[ \Gamma_{pg} = \frac{D_{gas} (n_{pls} - n_{gas})}{d_{gas}} \]

SMD: \[ \frac{\partial n_{pls}}{\partial t} = \sum_{j} R_{j} - \frac{1}{d_{pls}} \Gamma_{pg} \]

Neutral reactor: \[ \frac{\partial n_{gas}}{\partial t} = \sum_{j} R_{j} + \frac{1}{d_{gas}} \Gamma_{pg} \]

- electrons
- ions
- neutrals

- e.g. metal surface with diluted bacteria

- zero flux

- Computational domain

- \( d_{pls} \)

- \( d_{gas} \)

- SMD

- Neutral reactor

- Treated surface

- \( \Gamma_{pg} \)

- \( \Gamma_{pg} \)

- \( E \)

- 10 ns
SDBD: model description (2)

Computational domain

SMD

Neutral reactor

Treapped surface

e.g. metal surface with diluted bacteria

Zero flux

$\Gamma_{pg}

\begin{align*}
&\text{• electrons} \\
&\text{• ions} \\
&\text{• neutrals}
\end{align*}

E

10 ns

Negative particles: $e^-, O_2^-, O_3^-, O_4^-, H^-, OH^-, NO^-, N_2O^-, NO_2^-, NO_3^-$

Positive particles: $N^+, N_2^+, N_3^+, N_4^+, O^+, O_2^+, O_4^+, NO^+, N_2O^+, NO_2^+, H^+, H_2^+, H_3^+, OH^+, H_2O^+, H_3O^+$

Neutrals: $N, N^*, N_2, N_2^*, N_2^{**}, O, O^*, O_2, O_2^*, O_3, NO, N_2O, NO_2, NO_3, N_2O_5, H, H_2, OH, H_2O, HO_2, H_2O_2, HNO, HNO_2, HNO_3$
SDBD: multiple time-scale phenomena

- Electron impact reactions
- Charge transfer, ion recombination
- Neutral reactions
- Applied voltage period
- Gas diffusion
- Exposure time

Simulation procedure:

- SMD (electrons, ions, neutrals)
- Cycle-averaged reaction rates
- SMD (electrons, ions, neutrals)
- Neutral reactor (neutrals)
SDBD: dynamics of charged particles

Power density: 0.1 W/cm²
Frequency: 10 kHz
Gap distance: 1 mm
Humidity: 0% (dry)

Positive ions

Negative ions

Neutral

SMD
SDBD: comparison between dry and humid air

- **Power density**: 0.1 W/cm²
- **Frequency**: 10 kHz
- **Gap distance**: 1 mm
- **Humidity**: 0% (dry), 30% (humid)

The diagram shows the concentration levels of various gases under dry and 30% humidity conditions. The gases include H₂, N₂O, O₃, N₂O₅, NO, NO₂, NO₃, H₂O₂, OH, and HNO₂.
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Wound healing: model description

- 6-species PDEs in 1-D Cartesian coordinates
- modified parameters and additional terms for plasma treatment

**Major pathways for wound healing**
- bacteria
  - oxygen
- chemo-attractants
- capillary tips
- blood vessels
- fibroblasts
- ECM
Wound healing: governing equations (1)

- **Oxygen:** \( c \)

\[
\frac{\partial c}{\partial t} + \nabla \cdot (-D_c \nabla c) = -\left( \frac{k_1}{1 + k_b e} + k_2 e \right) \frac{c}{k_3 + c} - k_4 bc + k_5 b
\]

consumption by bacteria

- **Chemoattractants:** \( a \)

\[
\frac{\partial a}{\partial t} + \nabla \cdot (-D_a \nabla a) = -k_6 ab - k_7 a + \frac{k_8 H(c - c_L)H(c_H - c)}{1 + e}
\]

production
Wound healing: governing equations (2)

- **Capillary tips:** $n$

$$\frac{\partial n}{\partial t} + \nabla \cdot (-D_n \nabla n) = \nabla \cdot \left( \frac{-\kappa_n en}{(1 + e^2)(1 + a)^2} \nabla a \right) + a(k_9 b + k_{10} n) - n(k_{11} n + k_{12} b)$$

chemotaxis

- **Fibroblasts:** $f$

$$\frac{\partial f}{\partial t} + \nabla \cdot (-D_f \nabla f) = \nabla \cdot \left( \frac{-\kappa_f f}{(1 + a)^2} \nabla a \right) + \frac{k_{16} f c}{1 + c} - \frac{k_{17} f^2}{(1 + c)(1 + e)}$$

chemotaxis
Blood vessels: \( b \)

\[
\frac{\partial b}{\partial t} = -\frac{\kappa_n e n}{(1 + e^2)(1 + a)^2} \nabla a + k_{13} b (k_{14} e + k_{15} f - b)
\]

production by capillary tips

ECM: \( e \)

\[
\frac{\partial e}{\partial t} = k_{18} f c (k_{19} c - e)
\]

deposition
Wound healing: untreated wound

- oxygen
- chemoattractants
- capillary tips
- blood vessels
- fibroblasts
- ECM

$t = 0.0$ [week]
Wound healing: effects of gas plasmas

Twice/day plasma treatment
- 99% direct reduction ($R$)
- 90 min doubling time ($k_p$)

Oxygen: $c$

$$\frac{\partial c}{\partial t} + \nabla \cdot (-D_c \nabla c)$$

$$= -\left(\frac{k_1 P_n}{1 + k_be} + k_2 e\right) \frac{c}{k_3 + c} - k_4 bc + k_5 b$$

$$P_n = \frac{RP_{n-1} \exp(k_p t)}{1 + RP_{n-1} \{\exp(k_p t) - 1\}}$$
Wound healing: possible effects of gas plasmas

**direct effect (short-term)**

M. Pavlovich. (in preparation)

> 2-log reduction (99%)

**indirect effect (long-term)**


Inhibition of growth

(≈90min doubling time)
Wound healing: plasmas treatment

- oxygen
- chemoattractants
- capillary tips
- blood vessels
- fibroblasts
- ECM

$t = 0.0$ [week]
Wound healing: healing speed

Plasma-based wound treatment
- 99% direct reduction
- 90 min doubling time

![Graph showing fraction of wounded tissue over time for untreated and plasma treatment cases. The graph indicates a faster healing rate for the plasma treatment compared to the untreated case.](image)
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Concluding Remarks

1. Multi-species and multi-time step global model was developed for SMD. Our model shows that significant amount of bactericidal ROS/RNS are generated in SMD.

2. 6 species plasma-based wound healing model was developed based on Flegg’s model. Our model suggests that wound sterilization is a key mechanism of wound treatment by gas plasmas.
Acknowledgements

Prof. G. Morfill and the team plasma health care
(Max-Planck Institute, Germany)

Prof. D. Clark (UC Berkeley, USA)

Dr. M. Traylor (former postdoc at Graves group)
M. Pavlovich, S. Karim, and H. Pritha (Graves group)

Reviews for plasma medicine