Multiphysics Modeling of Ambient Gas Plasma-Based Wound Healing Process

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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

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

**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
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- tissue reorganization/realignment
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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
SMD (surface micro-discharge)  

- Power density: 0.1-1.0 W/cm$^2$
- Voltage: 10-20 kV$_{pk-pk}$
- Frequency: 1-10 kHz

Plasma dynamics/chemistry
Mass transportation

Plasma-biomaterial interaction

Mechano-chemical model of cell/tissue/system
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For charged particles: \( \Gamma_{pg} = 0 \)

For neutrals:
\[
\Gamma_{pg} = \frac{D_{gas} (n_{pls} - n_{gas})}{d_{gas}}
\]
SDBD: model description (2)

Computational domain

$\begin{align*}
\text{SMD} & \quad \text{Neutral reactor} \\
\text{zero flux} & \quad \text{zero flux}
\end{align*}$

e.g. metal surface with diluted bacteria

$\begin{align*}
\text{SMD} & \quad \text{Neutral reactor} \\
\text{zero flux} & \quad \text{zero flux}
\end{align*}$

Negative particles: e, O$^-$, O$_2^-$, O$_3^-$, O$_4^-$, H$^-$, OH$^-$, NO$^-$, N$_2$O$^-$, NO$_2^-$, NO$_3^-$

Positive particles: N$^+$, N$_2^+$, N$_3^+$, N$_4^+$, O$^+$, O$_2^+$, O$_4^+$, NO$^+$, N$_2$O$^+$, NO$_2^+$, H$^+$, H$_2^+$, H$_3^+$, OH$^+$, H$_2$O$^+$, H$_3$O$^+$

Neutrals: N, N*, N$_2$, N$_2^*$, N$_2^{**}$, O, O*, O$_2$, O$_2^*$, O$_3$, NO, N$_2$O, NO$_2$, NO$_3$, N$_2$O$_5$, H, H$_2$, OH, H$_2$O, HO$_2$, H$_2$O$_2$, HNO, HNO$_2$, HNO$_3$
SDBD: multiple time-scale phenomena

Simulation procedure

- Cycle-averaged reaction rates

SMD (electrons, ions, neutrals)

Neutral reactor ( neutrals)

SMD (neutrals)

SMD (electrons, ions, neutrals)

exposure time

gas diffusion

applied voltage period

neutral reactions

electron impact reactions

charge transfer, ion recombination

100 ns

1 ms

1 ms

1 s

100 s
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)
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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
- fibroblasts
- ECM
Wound healing: governing equations (1)

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

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

consumption by bacteria

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

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

production
Wound healing: governing equations (2)

- **Capillary tips:** \( n \)

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

- **Fibroblasts:** \( f \)

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

- **Chemotaxis**

- **Oxygen**

- **Chemotactants**

- **Capillary tips**

- **Blood vessels**

- **Fibroblasts**

- **ECM**
Wound healing: governing equations (3)

- **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

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

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

Time dependent bacterial load

**Oxygen:** $c$

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

\[
P_n = \frac{R P_{n-1} \exp(k_p t)}{1 + R P_{n-1} \{\exp(k_p t) - 1\}}
\]
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)

![Graph showing bacterial density vs. post-irradiation incubation time]

- Control
- Plasma
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
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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.
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Reviews for plasma medicine