Modeling and Simulation of Gas Plasma-assisted Wound Healing

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Outline

1. Introduction
   • Gas plasma-generated ROS/RNS
   • ROS/RNS in medicine

2. Modeling of wound healing
   • Current status
   • Modeling strategy
   • Model description
   • Simulation results

3. Concluding remarks
### Plasma-biomaterial interaction

**Plasmas in ambient air at room temperature**

![Diagram of plasma-biomaterial interaction]

<table>
<thead>
<tr>
<th>physics</th>
<th>chemistry</th>
<th>electrostatic</th>
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</table>
| • DNA damage  
• etching  
• sputtering | • oxidation  
• signaling | • membrane disruption (≈10^9 V/m)  
• stimulation |
ROS/RNS in gas plasmas and biomedicine

- **ROS** (reactive oxygen species): $O_2^-$, OH, HO$_2$, H$_2$O$_2$, O$_3$, O$_2$(1$\Delta$), etc.
- **RNS** (reactive nitrogen species): NO, NO$_2$, NO$_3$, HNO$_2$, N$_2$O$_4$, N$_2$O$_3$, etc.

- **Mass spectroscopy**

- **Phagocytes**
- **Antibiotics**
- **Radiation therapy**

Abbas, Celluar and Molecular Immunology (Elsevier, 2005).
ROS/RNS in biomedicine (3)

Cancer treatment

G. T. Wondrak, Antioxid Redox Signaling 11 (2009) 3013
ROS/RNS in biomedicine (4)


Wound healing

[Diagram showing stages of wound healing: Inflammation, Proliferation, Regeneration, with changes in the relative number of cells over time.]
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Plasma health care 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
General wound healing processes

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**
- ~ years
- tissue reorganization/realignment
- apoptosis of unnecessary cells
Known effects of gas plasmas in wound healing

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
**Strategy**

**SMD (surface micro-discharge)**  

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

![Diagram of SMD process](image)

- Plasma dynamics/chemistry
- Mass transportation
- Plasma-biomaterial interaction
- Mechano-chemical model of cell/tissue/system
Which ROS/RNS are generated from SMD?

- Power density: 0.1 W/cm²
- Frequency: 10 kHz
- Gap distance: 1 mm
- Humidity: 0% (dry), 30% (humid)
A few min treatment and weeks long effect?

- 1 ns: electron impact reaction
- 1 μs: ion recombination
- 1 ms: neutral reactions
- 1 s: exposure time
- 1 min: treatment period
- 1 hour
- 1 day: treatment period
- 1 week: immune response
- 1 month

**Wound** to **healed tissue**

- **Short-term**: disinfection
- **Long-term**: growth inhibition
Evidence of short-term effect

- frequency: 10 kHz
- voltage: $10 \, \text{kV} \, V_{\text{pkpk}}$
- power consumption: ~5 W
- distance to sample: 1 mm
- exposure time: 5 min

Sterilization on various surfaces

- SS: ~99.999%
- silicone: ~99.99%
- pig skin: ~99%

Sample surface
- SS mesh electrode
- glass plate
- Teflon
- copper electrode
- E. coli

Log reduction after 5 min treatment
Evidence of long-term effect (1)
Evidence of long-term effect (2)

Inhibition of growth (~90min doubling time)

Model description

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

![Diagram of major pathways for wound healing](image-url)

- bacteria
  - oxygen
- chemo-attractants
  - capillary tips
  - blood vessels
- fibroblasts
  - ECM
Governing equations (1)

- Oxygen: \( c \)

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

consumption by bacteria

- Chemoattractants: \( a \)

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

production
### Governing equations (2)

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

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

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

\[
\frac{\partial f}{\partial t} + \nabla \cdot (-D_f \nabla f) = \nabla \cdot \left( -\kappa_f \frac{f}{(1 + a)^2} \nabla a \right) + \frac{k_{16} fc}{1 + c} - \frac{k_{17} f^2}{(1 + c)(1 + e)}
\]
**Governing equations (3)**

- **Blood vessels:** \( b \)

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

production by capillary tips

- **ECM:** \( e \)

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

deposition
Simulation results: untreated wound

$t = 0.0$ [week]
Introducing plasmas treatment term

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

**Oxygen: $c$**

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

\[
P_n = \frac{R P_{n-1} \exp(k_{p} t)}{1 + R P_{n-1} \{ \exp(k_{p} t) - 1 \}}
\]
Simulation results: plasma-treated wound

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

$t = 0.0$ [week]
Simulation results: healing speed

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

Graph showing the fraction of wounded tissue over time for untreated and plasma treatment conditions.
Conditions for successful treatment

Normalized healing speed

Initial log reduction

Doubling time of bacteria [min]

non-infected wound (1.7 week)

fully infected wound (12.5 week)

90 min

2 log-reduction
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Concluding Remarks

1. 6-species 1-D plasma-assisted wound healing model was developed based on a previously published model.

2. We proposed short-term inactivation and long-term growth inhibition model. The successful treatment was observed under realistic parameter set.

3. Wound sterilization could be the dominant effect of gas plasmas treatment
Acknowledgements

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