Surface Microdischarges and Modeling Wound Healing

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Outline

1. Surface Microdischarges (SMD): Experiments and modeling

2. Modeling wound healing: a start

3. Where to go from here? A recent ‘breakthrough’ paper (journal *Cell*) suggests an orientation and hints at possible directions
Indirect Dielectric Barrier Discharges in Air

Surface microdischarge or SMD

Different type of model approach used to predict chemistry – dealing with highly disparate time scales
Plasma chemistry model of surface microdischarge in humid air and dynamics of reactive neutral species

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Figure 1. Schematic diagram of SMD (a) and photograph of emission from SMD (b).
discharge layer
(electrons, ions, neutrals)
\[ \frac{\partial n_p}{\partial t} = \sum_j k_j \prod n_{r,j} - \frac{\Gamma_{pg}}{d_p} \]

\[ \Gamma_{pg} = \frac{D(n_p - n_g)}{(d_p + d_g)/2} \]

neutral gas domain
(neutrals (b))
\[ \frac{\partial n_g}{\partial t} = \sum_j k_j \prod n_{r,j} + \frac{\Gamma_{pg}}{d_g} \]

\[ d_p = 0.1 \text{ mm} \]

\[ d_g = 10 \text{ mm} \]
Modeling: multiple time-scale phenomena

- 100 ns: electron impact reactions, charge transfer, ion recombination
- 1 ms: neutral reactions, applied voltage period, gas diffusion
- 1 s: exposure time

Simulation procedure:

SMD (electrons, ions, neutrals) → Cycle-averaged reaction rates → Neutral reactor (neutrals)
<table>
<thead>
<tr>
<th>Table 1. Chemical species included in our model.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positively charged particles</td>
</tr>
<tr>
<td>Negatively charged particles</td>
</tr>
<tr>
<td>Neutral species Group (a)</td>
</tr>
<tr>
<td>Neutral species Group (b)</td>
</tr>
</tbody>
</table>
Table 2. A list of reactions and the rate constants.

<table>
<thead>
<tr>
<th>Index</th>
<th>Reaction</th>
<th>Rate constant(^a)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R1)</td>
<td>( e + N_2 \rightarrow N(^{2}D) + N + e )</td>
<td>( 3.99 \times 10^{-17} \varepsilon^{2.24} \exp(-9.10/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R2)</td>
<td>( e + N_2 \rightarrow N_2(A^3\Sigma) + e )</td>
<td>( 3.34 \times 10^{-16} \varepsilon^{-0.06} \exp(-8.50/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R3)</td>
<td>( e + N_2 \rightarrow N_2(B^3\Pi) + e )</td>
<td>( 8.44 \times 10^{-15} \varepsilon^{-0.33} \exp(-9.15/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R4)</td>
<td>( e + N_2 \rightarrow N^+_2 + e + e )</td>
<td>( 1 \times 10^{-16} \varepsilon^{1.90} \exp(-14.6/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R5)</td>
<td>( e + N \rightarrow N(^{2}D) + e )</td>
<td>( 5.06 \times 10^{-15} \exp(-10.8/\varepsilon^{3.95}) )</td>
<td>b</td>
</tr>
<tr>
<td>(R6)</td>
<td>( e + N \rightarrow N^+ + e + e )</td>
<td>( 1.45 \times 10^{-17} \varepsilon^{2.58} \exp(-8.54/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R7)</td>
<td>( e + O_2 \rightarrow O + O + e )</td>
<td>( 2.03 \times 10^{-14} \varepsilon^{-0.10} \exp(-8.47/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R8)</td>
<td>( e + O_2 \rightarrow O(1D) + O + e )</td>
<td>( 1.82 \times 10^{-14} \varepsilon^{-0.13} \exp(-10.7/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R9)</td>
<td>( e + O_2 \rightarrow O_2(a^1\Delta) + e )</td>
<td>( 1.04 \times 10^{-15} \exp(-2.59/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R10)</td>
<td>( e + O_2 \rightarrow O_2^+ + e + e )</td>
<td>( 9.54 \times 10^{-12} \varepsilon^{-1.05} \exp(-55.6/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R11)</td>
<td>( e + O_3 \rightarrow O + O_2 + e )</td>
<td>( 1.78 \times 10^{-12} \varepsilon^{-0.614} \exp(-11.5/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R12)</td>
<td>( e + O \rightarrow O(1D) + e )</td>
<td>( 7.46 \times 10^{-15} \exp(-5.58/\varepsilon^{1.47}) )</td>
<td>b</td>
</tr>
<tr>
<td>(R13)</td>
<td>( e + O \rightarrow O^+ + e + e )</td>
<td>( 4.75 \times 10^{-15} \varepsilon^{0.61} \exp(-22.1/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R14)</td>
<td>( e + H_2O \rightarrow H_2O^+ + e + e )</td>
<td>( 9.65 \times 10^{-18} \varepsilon^{2.53} \exp(-8.99/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R15)</td>
<td>( e + H_2O \rightarrow OH^+ + H + e + e )</td>
<td>( 9.89 \times 10^{-12} \varepsilon^{-1.64} \exp(-67.6/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R16)</td>
<td>( e + H_2O \rightarrow H^+ + OH + e + e )</td>
<td>( 7.45 \times 10^{-15} \varepsilon^{0.34} \exp(-54.2/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R17)</td>
<td>( e + H_2O \rightarrow O^+ + H_2 + e + e )</td>
<td>( 7.4 \times 10^{-16} \varepsilon^{0.45} \exp(-55.5/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R18)</td>
<td>( e + H_2O \rightarrow H^+ + O + e + e )</td>
<td>( 8.49 \times 10^{-15} \varepsilon^{-1.23} \exp(-74.0/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R19)</td>
<td>( e + H_2O \rightarrow OH + H + e )</td>
<td>( 5.15 \times 10^{-15} \varepsilon^{0.62} \exp(-10.9/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R20)</td>
<td>( e + H_2O \rightarrow H + O )</td>
<td>( 5.19 \times 10^{-18} \varepsilon^{1.2} \exp(-13.8/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R21)</td>
<td>( e + H \rightarrow H + H + e )</td>
<td>( 3.29 \times 10^{-15} \varepsilon^{0.578} \exp(-7.56/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R22)</td>
<td>( e + H_2 \rightarrow H^+ + e + e )</td>
<td>( 4 \times 10^{-17} \varepsilon^{2.13} \exp(-14.9/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R23)</td>
<td>( e + N_2O_5 \rightarrow NO_2^+ + NO_3 + e + e )</td>
<td>( 2.43 \times 10^{-17} \varepsilon^{2.77} \exp(-5.62/\varepsilon) )</td>
<td>b</td>
</tr>
<tr>
<td>(R24)</td>
<td>( e + N^+ + M \rightarrow N + M )</td>
<td>( 3.12 \times 10^{-35}/T_e^{1.5} )</td>
<td>[9]</td>
</tr>
<tr>
<td>(R25)</td>
<td>( e + N_2^+ \rightarrow N + N )</td>
<td>( 1.66 \times 10^{-12}/T_e^{0.7} )</td>
<td>[9]</td>
</tr>
<tr>
<td>(R26)</td>
<td>( e + N_2^+ \rightarrow N(^{2}D) + N )</td>
<td>( 1.5 \times 10^{-12}/T_e^{0.7} )</td>
<td>[9]</td>
</tr>
<tr>
<td>(R27)</td>
<td>( e + N_3^+ + M \rightarrow N_2 + M )</td>
<td>( 3.12 \times 10^{-35}/T_e^{1.5} )</td>
<td>[11]</td>
</tr>
<tr>
<td>(R28)</td>
<td>( e + N_2^+ + M \rightarrow N_2 + N )</td>
<td>( 3.46 \times 10^{-12}/T_e^{0.5} )</td>
<td>[11]</td>
</tr>
<tr>
<td>(R29)</td>
<td>( e + N_2^+ + M \rightarrow N_2 + N )</td>
<td>( 4.73 \times 10^{-11}/T_e^{0.53} )</td>
<td>[11]</td>
</tr>
<tr>
<td>(R30)</td>
<td>( e + O^+ + M \rightarrow O + M )</td>
<td>( 3.12 \times 10^{-35}/T_e^{1.5} )</td>
<td>[9]</td>
</tr>
<tr>
<td>(R31)</td>
<td>( e + O_2^+ \rightarrow O + O )</td>
<td>( 1.68 \times 10^{-11}/T_e^{0.7} )</td>
<td>[11]</td>
</tr>
<tr>
<td>(R32)</td>
<td>( e + O_2^+ \rightarrow O + O(1D) )</td>
<td>( 1.24 \times 10^{-11}/T_e^{0.7} )</td>
<td>[11]</td>
</tr>
</tbody>
</table>
Charged Species in Discharge Layer During Pulse
Neutral Species in Discharge Layer During Pulse

(a) O, O$_2^*$, O$_3$

(b) N, N$_2^*$, N$_2^{**}$

(c) N$_2O$, N$_2O_5$, NO, NO$_3$

(d) H, H$_2$O, H$_2$O$_2$, HNO$_3$, HO$_2$, OH
Time Evolution of Neutral Species in Diffusion Layer
Cycle-Averaged Neutral Species

Discharge region

- $H_2$
- N
- O
- OH
- NO
- $O_2(a^1\Delta)$
- $H_2O_2$
- $N_2O$
- $NO_2^+$
- $NO_2$
- $NO_3^-$
- $HNO_2$
- $O_3$
- $N_2O_5$

Diffusion region

- $H_2$
- $H_2O_2$
- $N_2O$
- $O_3$
- $HNO_2$
- $NO_2$
- $NO_3$
- $N_2O_5$
Quantification of FTIR measurement
(thanks to: T. Ichino, preliminary)

- Power: 0.05 W/cm² (low power) and 0.3 W/cm² (high power)
- Humid air at 1 atm
- Gas temperature: 300 K
- Measured for 2-3 min after SMD ignition

<table>
<thead>
<tr>
<th></th>
<th>0.05 W/cm²</th>
<th>0.3 W/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₃</td>
<td>1000</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>HNO₃</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>NO₂</td>
<td>&lt;10</td>
<td>300</td>
</tr>
<tr>
<td>N₂O</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>N₂O₅</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>&lt; 10</td>
<td></td>
</tr>
</tbody>
</table>
First comparisons…

But note NO$_2$ model prediction (~ 1 ppm) currently is well below measurement (~ 300 ppm)
FAST TRACK COMMUNICATION

Long-term antibacterial efficacy of air plasma-activated water

Matthew J Traylor, Matthew J Pavlovich, Sharmin Karim, Pritha Hait, Yukinori Sakiyama, Douglas S Clark and David B Graves

\[ \text{log reduction} = \log_{10} \left( \frac{\text{initial number}}{\text{number of survivors}} \right) \]
Effect of Discharge Parameters and Surface Characteristics on Ambient-Gas Plasma Disinfection

Matthew J. Pavlovich, Zhi Chen, Yukinori Sakiyama, Douglas S. Clark, David B. Graves*

Figure 6. Bacterial killing on several test surfaces. Surfaces were exposed to indirect-mode plasma for 60 s (black bars) and 300 s (white bars). Discharge power density was fixed at 0.75 W · cm⁻².

Figure 7. Comparison of plasma disinfection to other disinfectants. Surfaces were exposed for 60 s (black bars) and 300 s (white bars). Plasma, indirect-mode plasma; EtOH, 70% ethanol in water; CHX, chlorhexidine digluconate in water. 2% chlorhexidine showed complete disinfection within the detection limit.
The dynamics of ozone generation and mode transition in air surface micro-discharge plasma at atmospheric pressure

Tetsuji Shimizu\textsuperscript{1,3}, Yukinori Sakiyama\textsuperscript{2}, David B Graves\textsuperscript{2}, Julia L Zimmermann\textsuperscript{1} and Gregor E Morfill\textsuperscript{1}

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\textsuperscript{2} University of California, Berkeley, Berkeley CA 94720, USA
E-mail: tshimizu@mpe.mpg.de
Experimental schematic

- Orifice
- Fiber
- Ceramic plate/agar plate
- Quartz tube
- Ozone measurement line
- Stainless steel mesh grid
- Aluminum electrode
- Ceramic plate
- 26 mm in diameter
- 5 mm
- H.V.
- Ar/Hg lamp
- Quartz tube
- Plasma discharge

Diagram shows an experimental setup with various components and dimensions.
Figure 2. (a) Time evolution of ozone density ($n_{O_3}$) under different power inputs. (b) Time evolution with power input of 0.56 W/cm² and higher. The applied voltage was 15 kV$_{pp}$. 
$O_3$ correlates with bactericidal effects observed

Figure 4. Bactericidal effect of the SMD plasma and averaged ozone density for the first 30 s at different input powers. The applied voltage was 5, 10 and 15 kV$_{pp}$, but the results scaled only with power density under these conditions.
Ozone Correlates with Antibacterial Effects from Indirect Air Dielectric Barrier Discharge Treatment of Water

Matthew J Pavlovich, Hung-Wen Chang, Yukinori Sakiyama, Douglas S Clark, David B Graves

![Diagram of indirect air dielectric barrier discharge treatment of water]

- **NO₂⁻**
- **NO₃⁻**

![Graph showing concentration of NO₂⁻ and NO₃⁻ vs. power density (W/cm²)]

- **H₂O₂**

![Graph showing concentration of H₂O₂ vs. power density (W/cm²)]

- **O₃**

![Graph showing concentration of O₃ vs. power density (W/cm²)]
E coli Suspension tests 5 second contact time

Buffered and unbuffered: pH not important

$0.4 \text{ W/cm}^2$

$0.05 \text{ W/cm}^2$

E coli Suspension tests 5 second contact time

Buffered and unbuffered: pH not important

$0.4 \text{ W/cm}^2$

$0.05 \text{ W/cm}^2$
Concluding Remarks: SMD

1. Gas phase models are in reasonable preliminary agreement with measurements, but much more detailed study needed.

2. Ozone (low power mode) and nitrogen dioxide (high power mode) are predicted to be key gas phase species in SMD air plasmas.

3. Gas convection in general is likely to be important; certainly liquid transport effects can be dominant – recall need for vortexing.

4. Gas exchange with environment is important – e.g. enclosed vs. non-enclosed geometry strongly alters results.

5. *We have been consistently surprised by the subtleties of atmospheric pressure air DBD plasmas!*
Wound healing modeling: investigating ambient gas plasma treatment efficacy

Marat Orazov, Yukinori Sakiyama and David B Graves

\[
\frac{\partial c}{\partial t} = D_c \nabla^2 c - \left( \lambda_1 e + \lambda_2 \left( \frac{P(t)}{1 + \lambda_4 \rho} \right) \right) \frac{c}{\lambda_3 + c} - \lambda_4 b c + \lambda_5 b.
\]
Coupling plasma and wound

But how to couple plasma model with tissue/wound model??
Hypothesis: Plasma speeds healing by killing bacteria and increasing O$_2$ availability

- 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

bacteria → oxygen → chemo-attractants → fibroblasts → ECM
Wound healing: governing equations (1)

**Oxygen: c**

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

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
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: \( f \)**

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

chemotaxis
Wound healing: 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
Wound healing: infected, *untreated wound*

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

$t = 0.0$ [week]

(normalized variables)

(position)

Wound

Healed tissue
Wound healing: effects of gas plasmas

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

Oxygen: $c$

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

$$P_n = \frac{RP_{n-1} \exp(k_p t)}{1 + RP_{n-1} \{\exp(k_p t) - 1\}}$$

Time dependent bacterial load

Fraction of bacterial load

Fraction of bacterial load

Time [d]
Wound healing: with plasma treatment

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

$t = 0.0$ [week]
Model prediction of plasma effect on wound healing for infected wound

Plasma effects on bacteria:
- 99% direct reduction
- 90 min doubling time

![Graph showing the effect of plasma treatment on bacterial load and wounded tissue over time.](image)
1. Wound healing model is obviously relatively crude:
   - e.g. quantities treated as constant parameters are no doubt in reality varying with treatment
   - only a small fraction of relevant processes included in model

2. Effort was made to get consistent parameters from literature

3. Bacterial regrowth kinetics important

4. RONS from plasma directly kill wound surface bacteria but other effects probably important too:
   - protein/lipid reactions; gene expression
   - macrophages & inflammation processes…others…

Direct experimental measurements in vivo are crucial for future progress
A Whole-Cell Computational Model Predicts Phenotype from Genotype

Jonathan R. Karr,1,4 Jayodita C. Sanghvi,2,4 Derek N. Macklin,2 Miriam V. Gutschow,2 Jared M. Jacobs,2 Benjamin Bolival, Jr.,2 Nacyra Assad-Garcia,3 John I. Glass,3 and Markus W. Covert2,∗

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http://dx.doi.org/10.1016/j.cell.2012.05.044

Understanding how complex phenotypes arise from individual molecules and their interactions is a primary challenge in biology that computational approaches are poised to tackle. We report a whole-cell computational model of the life cycle of the human pathogen Mycoplasma genitalium that includes all of its molecular components and their interactions. An integrative approach to modeling that combines diverse mathematics enabled the simultaneous inclusion of fundamentally different cellular processes and experimental measurements. Our whole-cell model accounts for all annotated gene functions and was validated against a broad range of data. The model provides insights into many previously unobserved cellular behaviors, including in vivo rates of protein-DNA association and an inverse relationship between the durations of DNA replication initiation and replication. In addition, experimental analysis directed by model predictions identified previously undetected kinetic parameters and biological functions. We conclude that comprehensive whole-cell models can be used to facilitate biological discovery.
Figure 1. *M. genitalium* Whole-Cell Model Integrates 28 Submodels of Diverse Cellular Processes

(A) Diagram schematically depicts the 28 submodels as colored words—grouped by category as metabolic (orange), RNA (green), protein (blue), and DNA (red)—in the context of a single *M. genitalium* cell with its characteristic flask-like shape. Submodels are connected through common metabolites, RNA, protein, and the chromosome, which are depicted as orange, green, blue, and red arrows, respectively.
(B) The model integrates cellular function submodels through 16 cell variables. First, simulations are randomly initialized to the beginning of the cell cycle (left gray arrow). Next, for each 1 s time step (dark black arrows), the submodels retrieve the current values of the cellular variables, calculate their contributions to the temporal evolution of the cell variables, and update the values of the cellular variables. This is repeated thousands of times during the course of each simulation. For clarity, cell functions and variables are grouped into five physiologic categories: DNA (red), RNA (green), protein (blue), metabolite (orange), and other (black). Colored lines between the variables and submodels indicate the cell variables predicted by each submodel. The number of genes associated with each submodel is indicated in parentheses. Finally, simulations are terminated upon cell division when the septum diameter equals zero (right gray arrow).
Concluding Remarks: future of coupled plasma-biological system models

Incorporating such complex models of a cell/tissue to plasma models is probably unrealistic, certainly any time soon.

However, coupling plasma models to models of lipid bilayers or to model biofilms or model wounds seems possible and realistic.

We should think about (model) experimental systems that can be intelligently coupled with plasma models!
The emerging role of reactive oxygen and nitrogen species in redox biology and some implications for plasma applications to medicine and biology

David B Graves

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