CHALLENGES IN MODELING OF PLASMA INTERACTIONS IN MEDICINE AND BIOLOGY: WHAT INSIGHTS CAN YOU EXPECT?*

Natalia Yu. Babaeva

University of Michigan
Department of Electrical Engineering and Computer Science
Ann Arbor, MI 48109 USA http://uigelz.eecs.umich.edu
nbavaeva@umich.edu

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AGENDA

• Introduction to Plasma Medicine
• Plasma Sources - Direct and Indirect
• Status of the field
• Results from computer modeling of plasma-tissue interactions
• Concluding Remarks and Outlook
LOW TEMPERATURE PLASMA MEDICINE

- Atmospheric pressure LTPs directly on living tissue provides therapeutic value:
  - Skin ulcers
  - Melanoma treatment
  - Wound sterilization and healing
- APPs to deactivate bacteria and viruses on surfaces and in air.
- Plasma interaction with and delivery of activation to surfaces proceeds through multiple channels whose dominance depends on the plasma source:
  - Neutral Radicals [reactive O species (ROS), reactive N species (RNS)]
  - Ions (low and high energy)
  - Photons
  - Electric Fields
- The selectivity, reproducibility and therapeutic potential of plasma medicine are predicated on controlling delivery of this activation energy.

Ref: Prof. R. Hicks, University of California, USA

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PLASMA MEDICINE: WOUND HEALING

- Clinical trials in wound healing using remote plasma source.
- Max Planck Institute for Extraterrestrial Physics and Biochemistry

MicroPlaSter Clinical Trial (Phase-II) - Improved Wound Healing

With plasma treatment

Control without plasma treatment (second wound of same patient)

Before 1st treatment

Before 1st treatment

After 38 treatments

After 38 treatments

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PLASMA SOURCES: INDIRECT AND DIRECT TREATMENT

- The beneficial use of plasmas in medicinal therapies depends on the ability to reproducibly deliver to the tissue plasma generated
  - Radicals
  - Ions
  - Electric fields
  - Activation energy

- There are several scenarios whereby those species may be delivered:
  - Remote plasma jets (RPJs) in the direct vicinity of the tissue
  - Directly when the plasma is in contact with the tissue.

- The ability to control the reactive fluxes of these species varies by the plasma source.
REMOTE PLASMA SOURCES: JETS

- Remote plasma sources come in many configurations.
- One class of APP is a remote plasma jet. The plasma is sustained upstream of the surface being treated.

- Reactive species to the surface is dominated by neutral radicals, with a smaller contribution from charged species and photons.
- Interaction of activated injected gases with room air determine fluxes of reactive species to surface.


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A common plasma source at atmospheric pressure is a dielectric barrier discharge.

Plasma is directly applied to human tissue.

Electrodes covered by a dielectric with gaps of a few mm - dc current cannot pass through the dielectric.

Multiple streamers (100s μm diameter) propagate across gap.

10-50 kV (in air) at 10s of kHz – positive and negative polarity.

Individual filaments are a few ns in duration and statistically distributed.


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PLASMA STERILIZATION OF SURFACES

- Low-temperature non-equilibrium atmospheric pressure plasmas have proven to be robust tools for sterilization and decontamination.
  - Access into narrow and confined spaces, small cracks and microscopic openings where bacteria may reside.
  - Bacteria deactivation with plasmas is rapid.
- Sterilization results from same radicals and activation energy that produces therapeutic effects in plasma medicine.
  - ROS and RNS species, ground and excited states
  - Energetic ions
  - UV light
  - Large electric fields in the context of electroporation
- A variety of different types of plasma sources have been used for sterilization, which provide different combinations of chemically active neutral and charged species.
MODELING OF PLASMA BULLET PROPAGATION

- Multidimensional modeling by Sakiymana and Graves of plasma jets incorporate the mixing of injected gases with air.

- Production of RNS is largely attributed to reactions between plasma excited species and $N_2$ from air in mixing zones.

- Time-averaged relative emission profiles from $N_2$.


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MODELING OF PLASMA BULLET PROPAGATION

- 2D axially symmetric streamer model by Naidis, accounting for variation of helium–air mixture composition in the jet.
- Plasma parameters have a ring-shaped structure, typical for plasma bullets.

- Normalized $N_2$ emission.
- $N_e$ and $N_2(C^3\Pi)$ at different axial positions

Plasma treatment of living tissue is based on controlling plasma sources to deliver the desired fluxes of radicals and ions to surfaces.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important for wound healing, sterilization and cancer treatment.

Challenges:

- It is not clear which species and in what proportions are optimum for each type of treatment.
- More complex situation when considering the UV photons, energetic ions and electric fields produced by the discharge which also interact with the tissue.
- Complexity and interdependencies: Surrounding materials can significantly affect plasma parameters - the shape of the wound and the permittivity of the fluid in a wet wound can warp local electrical fields which then feed back to the plasma.
- Large dynamic ranges, poorly known chemistries.
• Plasmas for medicine have vastly different timescales that must be addressed in models.

• Integrating timestep: $\Delta t$
• Dynamic timescale: $\Delta T$

• Plasma transport:
  • Dielectric relaxation
    $\Delta t = \varepsilon/\sigma \sim 1 \text{ ps} - 10 \text{ ns}$
  • $\Delta T = \text{ns} - \text{ms}$

• Surface chemistry:
  • $\Delta t = \mu s$, $\Delta T = 10 \text{ s}$

• Also, microns to meters..

• Certain phenomena tightly coupled and must be integrated in lockstep.

• Those less coupled can be addressed with time slicing.
MODELING PLATFORM: \textit{nonPDPSIM}

- Poisson’s equation: \( \nabla (\varepsilon \nabla \Phi) = -\left( \sum_j q_j N_j + \rho \right) \)

- Transport of charged and neutral species: \( \frac{\partial N_j}{\partial t} = -\nabla \cdot \bar{\Gamma} + S \)
  - Charged Species: \( \bar{\Gamma} = \text{Sharffeter-Gummel} \)
  - Neutral Species: \( \bar{\Gamma} = \text{Diffusion} \)

- Surface Charge: \( \frac{\partial \rho}{\partial t} = \left[ \sum_j q_j \left( -\nabla \bar{\Gamma} + S \right) - \nabla (\sigma(-\nabla \Phi)) \right]_{\text{material}} \)

- Electron Temperature (transport and rate coefficients from 2-term spherical harmonic expansion solution of Boltzmann’s Eq.): \( \dot{\left( \frac{3}{2} n_e k T_e \right)} / \partial t = S(T_e) - L(T_e) - \nabla \cdot \left( \frac{5}{2} \Phi k T_e - \kappa(T_e) \cdot \nabla T_e \right) \)

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MODELING PLATFORM: *nonPDPSIM*

- Radiation transport and photoionization:

\[
S_m(\vec{r}_i) = N_m(\vec{r}_i) \cdot \sum_k \sigma_{mk} A_k \int N_k(\vec{r}_j') G_k(\vec{r}_j', \vec{r}_i) d^3\vec{r}_j' \quad \text{with} \quad G(\vec{r}_j', \vec{r}_i) = \exp\left(-\sum_l \sigma_{lk} N_l(\vec{r}_j') d\vec{r}_j'\right) / \left(4\pi|\vec{r}_j' - \vec{r}_i|^2\right)
\]

- Solid materials represented as lossy dielectrics with differentiated regions having specified permittivity \(\varepsilon\) and conductivity \(\sigma\).

- Poisson’s equation extended into materials.

\[
\nabla(\varepsilon \nabla \Phi) = -\rho \\
\frac{\partial \rho}{\partial t} = \sum_j \left(-\nabla \cdot q_j \tilde{\Gamma}_j\right)_{\text{surface}} - \nabla\left(\sigma (-\nabla \Phi)\right)
\]

- Solution: 1. Unstructured mesh discretized using finite volumes.
  2. Fully implicit transport algorithms with time slicing between modules.

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nonPDPSIM: NEUTRAL FLUID TRANSPORT

- Fluid averaged values of mass density, mass momentum and thermal energy density obtained using unsteady, compressible algorithms.

\[
\frac{\partial \rho}{\partial t} = -\nabla \cdot (\rho \vec{v}) + (\text{inlets, pumps})
\]

\[
\frac{\partial (\rho \vec{v})}{\partial t} = \nabla (NkT) - \nabla \cdot (\rho \vec{v} \vec{v}) - \nabla \cdot \vec{\mu} + \sum_i q_i N_i \vec{E}_i
\]

\[
\frac{\partial (\rho c_p T)}{\partial t} = -\nabla (-\kappa \nabla T + \rho \vec{v} c_p T) + P_i \nabla \cdot \vec{v}_f - \sum_i R_i \Delta H_i + \sum \vec{j}_i \cdot \vec{E}
\]

- Individual neutral species diffuse within the single fluid, and react with surfaces

\[
\frac{\partial N_i}{\partial t} = -\nabla \cdot (N_i \vec{v}) - \nabla \cdot (-D_i \nabla N_i) + S_i
\]
ION ENERGY-ANGULAR DISTRIBUTIONS TO TISSUE

- IEADs to surfaces obtained with Plasma Chemistry Monte Carlo Module.
- Structured PCMC mesh overlayed onto unstructured fluid mesh – E-fields interpolated onto mesh
- Pseudo-particles are launched from sites near surface determined by sources in and fluxes into mesh.
- Monte Carlo techniques advance trajectories in time varying E-fields while accounting for collisions.
- The energy and angles of particles as they strike surfaces are recorded.
## GAS PHASE HUMID AIR PLASMA CHEMISTRY

- **N<sub>2</sub>, O<sub>2</sub>**
  
  \[
e + N_2 \rightarrow N_2(\nu) + e \\
e + N_2 \rightarrow N_2(A) + e \\
e + N_2 \rightarrow N + N + e \\
e + N_2 \rightarrow N_2^+ + e + e \\
e + O_2 \rightarrow O_2(\nu) + e \\
e + O_2 \rightarrow O_2(^1\Delta) + e \\
e + O_2 \rightarrow O + O + e \\
e + O_2 \rightarrow O_2^+ + e + e \\
e + O_2 \rightarrow O^- + O \\
e + O_2 + M \rightarrow O_2^- + M
\]

- **H<sub>2</sub>O**
  
  \[
e + H_2O \rightarrow OH + H + e \\
e + H_2O \rightarrow OH^- + H \\
e + H_2O \rightarrow O^- + H_2 \\
e + H_2O \rightarrow H_2O(v) + e \\
e + H_2O \rightarrow H_2O^+ + e + e \\
e + H_2O^+ \rightarrow H + OH \\
e + H_2O \rightarrow H_2O^+ + e + e \\
e + H_2 \rightarrow H + H + e
\]

- Full plasma chemical reaction mechanism is included in the model for interpulse period. During short pulses (< 5 ns), little gas phase chemistry occurs - major reactions are electron impact.

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DIELECTRIC BARRIER DISCHARGE TREATMENT OF WOUNDS AND BACTERIA CONTAMINATED SURFACES
MODEL OF HUMAN SKIN

- Thumb is treated as a floating electrode – right side is in contact with ground.
- Cellular structure is resolved in numerical mesh.
- Local $\varepsilon$ and $\sigma$ represent the electrical properties of the intra- and inter-cell structures.
### RANGE OF CELLS PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>Dead Cells</th>
<th>Cell membrane</th>
<th>Cytoplasm</th>
<th>Nuclear Envelope</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\varepsilon/\varepsilon_0)</td>
<td>3</td>
<td>5.8</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>(\sigma \text{ (}\Omega^{-1} \text{ cm}^{-1}))</td>
<td>(10^{-8})</td>
<td>(8.7 \times 10^{-8})</td>
<td>(4.8 \times 10^{-3})</td>
<td>(3.0 \times 10^{-5})</td>
</tr>
<tr>
<td>(\tau \text{ (s)})</td>
<td>(2.7 \times 10^{-5})</td>
<td>(5.9 \times 10^{-6})</td>
<td>(5.5 \times 10^{-10})</td>
<td>(5.9 \times 10^{-8})</td>
</tr>
</tbody>
</table>

- Local \(\varepsilon\) and \(\sigma\) represent the electrical properties of the intra- and inter-cell structures.
- Wide range of properties cited in literature - values used are “mid-range”
- Pulses shorter than dielectric relaxation time allow electric field penetration into tissue.

ELECTROPORATION

- Cell membranes are punctuated by pores and ion channels that regulate transport into-and-out-of cell.
- Intra-cell currents produced by E-fields accumulate charges and voltage across membranes.
- 0.1 – 1 V across membranes of 10s to 100s ns (>100 kV/cm) produce electroporation, an increase in the size of the pores.
- Fast rising E-fields (ns) can penetrate into cells, affecting cellular structures.

- Double-shell model of a cell and equivalent circuit.
- MD predication of pore formation

• Filaments are simultaneously launched with electron emission from dielectric – sustained by secondary emission by photons, ions.

• Photons may originate from other filament.

• In negative corona, negative space charge and on surface produces mutual repulsion and lateral forces.

• 1.2 mm, air, 1 atm, -20 kV

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**SIMULTANEOUS FILAMENTS IN DBD**

**Electron Density** $3.2 \times 10^{13}$ cm$^{-3}$ (2 dec)

- Negative Charges $5 \times 10^{12}$ cm$^{-3}$

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**Animation Slide**
NON-SIMULTANEOUS FILAMENTS

- Filaments are randomly (?) generated in DBD – timing of filaments is important.
- Competition between filaments due to residual charges on dielectric from previous filaments.
- Later filaments develop slowly and are less intense.
- 1.2 mm, air, 1 atm, -20 kV

Animation Slide

- 0.0 to 4.2 ns
TREATMENT OF “REAL” THUMB SURFACE

- Real thumb surface has variable gap distance.
- End filament reaches the surface later due to larger gap and negative space charge of earlier arrivals.
- The end filament tends to move laterally trying to reorient perpendicular to surface.
- 1.2 mm, air, 1 atm, -20 kV

• 0.0 to 5.0 ns

Animation Slide
**DEPOSITED CHARGES AND INDUCED CHARGING**

- Positive charge \((10^{15} \text{ cm}^{-3})\)

- Positive and negative charges accumulate on opposite sides of cells and membranes prior to streamer arrival.

- Surface charges negative upon arrival of streamer.

- Charging produces large E-fields in cells.

- Air, 1 atm, -30 kV

- 0.1 to 1.1 ns

- Negative charge \((10^{15} \text{ cm}^{-3})\)
ELECTRIC FIELD INSIDE TISSUE

- Initial E-field due to displacement current.
- With arrival of streamer, charging produces E-fields inside tissue > 170 kV/cm.
- Smaller E-fields in cytoplasma and nuclei – larger across membranes.
- Electroporation producing values.
- Air, 1 atm, -30 kV
DBD INTERACTIONS WITH WOUNDED SKIN
DBD INTERACTION WITH WET AND DRY WOUNDS

- Represent “dry wound” by cut into skin.
- Wet wound – plasma is in contact with blood serum.

• “Dry” Wounded skin

• “Wet” Wounded skin

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DRY WOUNDED SKIN: FIELDS AND CHARGES

- E-field (5 to 310 kV/cm)

- Debye length of many $\mu m$ enables penetration of plasma into wound – at cellular level.

- Radicals and ions are produced directly in wound.

- Negative charging of high capacitance cell membranes produces large intra-cellular E-fields (up to 300 kV/cm).

- Electroporation in addition to radicals and UV may be important.

- Humid Air (1% H$_2$O), 1 atm, -40kV

- 0.2 to 0.4 ns
WOUNDED SKIN: FLUXES 0.5 ns

- High $T_e$ inside wound.
- Increased electron impact sources due to electric field enhancement near cell edges.
- Photon fluxes in excess of $3 \times 10^{13} \text{ cm}^{-2}$ (100s of photons onto a single cell during one pulse).
- Cells are shadowed by neighbors while vertex receives high fluxes.
- Negative corona in Air, -40 kV

Log scale

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On a longer-time scale radicals can diffuse in (or out!) of the wound.

Radicals produced by electron impact in the wound diffuse out (or react away), such as O.

Radicals produced by subsequent reactions (e.g., NO) diffuse into the wound.

End result is integrated fluxes of RNS and ROS of comparable magnitude.

- Negative corona in Air, - 40 kV
For larger wounds a few layers of collagen and elastic fiber cells under the wound are resolved.
The interaction of streamers with wounds is synergistic.

The electrical properties of the wound (e.g., dry or filled with fluid) can dramatically influence the streamer even far from the wound.

Vacuum potentials and electric field lines are perturbed far from wound depending on size and permittivity of fluid in wound.

This in turn affects the streamer treatment of the wound.

- Humid air, 1 atm, -30 kV
LARGE WOUND: ELECTRON DENSITY

- Slowing of streamer; reduction in density and spreading with high $\varepsilon$.
- With radius of streamer less than wound, streamer is “confined”.
- Humid air, 1 atm, -30 kV

MIN Log scale MAX

Animation Slide

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BLOOD PLATELETS IN PLASMA

- Platelets are irregularly-shaped anuclear cell fragments 2-3 µm in size in plasma.
- At the initial stage of wound healing there is an increased aggregation of platelets to enable the wounded vessels to complete the clotting process.
- Platelets also release cytokines (growth factors) that signal cells to participate in later phases of healing.
- Plasmas have been shown to speed wound healing though the mechanism is not clear – one possible mechanisms plasma activation of blood platelets.
EPIDERMIS WOUNDS WITH PLATELETS: E-FIELDS

- Wet wound $\varepsilon/\varepsilon_0=80$ with Platelets

Electric fields delivered through blood serum to underlying cells are 50-100 kV/cm.

- Irregularly shaped platelets intensify local electric fields.

- Humid Air, $\varepsilon/\varepsilon_0=80$ with platelets.

- Electric Field (kV/cm)
- Electric Field 20-300 kV/cm
- Irregularly shaped platelets intensify local electric fields.
- Depletion of electric field near poles and enhancement near the equators of the platelets.
- E-field enhancement in tissue under liquid.
- Humid Air, -30 kV
- Animation 0.1-0.46 ns

- Blood-plasma $\varepsilon/\varepsilon_0 = 27$, Platelets $\varepsilon/\varepsilon_0 = 6$
DIRECT PLASMA TREATMENT OF BACTERIA CONTAMINATED ROUGH SURFACES
Examine DBD treatment of rough surface with bacteria.

Bacteria in “nooks-and-crannies” of surfaces will receive energetic fluxes in part proportional to their view angle.

Humid air \( (\text{N}_2/\text{O}_2/\text{H}_2\text{O} = 79/20/1) \), 1 atm
PROPERTIES OF SINGLE FILAMENT IN DBD

- Electron density (cm\(^{-3}\)) and Potential (kV)

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<tbody>
<tr>
<td>0.37 ns 4x10(^{14}) cm(^{-3})</td>
<td>0.41 ns 7x10(^{14}) cm(^{-3})</td>
<td>0.5 ns 2x10(^{15}) cm(^{-3})</td>
<td>0.5 ns 2x10(^{16}) cm(^{-3})</td>
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<tr>
<td>Rough Surface with Bacteria</td>
<td>Rough Surface with Bacteria</td>
<td>Rough Surface with Bacteria</td>
<td>Rough Surface with Bacteria</td>
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<tr>
<td>Polymer</td>
<td>Grounded Electrode</td>
<td>Grounded Electrode</td>
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</table>

- Filament is launched with electron emission from dielectric – sustained by secondary emission by photons, ions.
- The electric potential is compressed in front of the filament resulting in an enhanced electric field.
- Charge separation in head of the streamer produces large E-field (10s – 100 kV/cm).
- Filament spreads over the surface.

- 1 mm, humid air (1% H\(_2\)O), 1 atm, -15 kV
RADICALS: PRODUCTION vs LONG TERM DIFFUSION

- **0.5 ns**
  - Initial production of radicals in the streamer channel is by electron impact dissociation on ns time-scale.
  - Long term diffusion redistributes the radical density while reactions (e.g., $O \rightarrow O_3$) take place.
  - Initially non-uniform distribution is homogenized by overlap of contributions from multiple streamers.

- **1 ms**

- **1 mm, humid air, 1 atm, -15 kV**
LOCAL STRUCTURE- CHARGING, SHADOWING

- **Electron Density**

  - Humid air, 1 atm, -15 kV

- **Electric Field**

  - Debye lengths of 0.5 to 1 µm and enables penetration into roughness.
  - The electric field is enhanced near the convex edges and depleted near the concave valleys.
  - Electric field as high as 700 kV/cm can be induced by the approaching DBD filament.

- **Negative Charge**

  - Debye lengths of 0.5 to 1 µm and enables penetration into roughness.

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• Humid air, 1 atm, -15 kV

• Short term production is nonuniform on the scale of the roughness and bacteria.

• Long term diffusion enables uniform penetration of radicals into surface roughness with uniformity of a few percent.
**RADICALS, IONS, PHOTONS - MICROSCALE**

- Radical Fluxes (cm\(^{-2}\)s\(^{-1}\))
- Ion Fluxes
- Photon Fluence

**Humid air, 1 atm, -15, -20, -30 kV**
- 1 ms

Neutral radicals eventually homogenize and diffuse into nooks-and-crannies – fluxes depend on voltage, temperature
- Ion fluxes sensitive to topology due to surface charging.
- Photon fluxes sensitive due to line-of-site.

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POSITIVE STREAMER PLASMA INTO TRENCHES

\([O_2^+]\) (cm\(^{-3}\), 3 dec)

- **AR = 20**
  - Plasma spreads over the dielectric simultaneously with penetration into trenches. Larger capacitance slows streamer.
  - **AR = aspect ratio [depth of trench]/[width]**
  - **20kV, Positive streamer**

- **AR = 50**

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**Animation Slide**

Log scale

MIN

MAX

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Filament squeezing through the trench carries high electric field located predominantly near the head and walls (sheath region).
Faster plasma penetration for wider trenches. No penetration for 3 µm trench.
While squeezing through the trench, the filament advances high electric field along the walls.

Intensive etching of walls and bottom surfaces.

- Snap shop at 0.33 ns
- Animation 0.2 - 0.7 ns
Thermalized ions before IW arrives, quick rise in energy when front arrives, subsequent IEAD stabilization for a few ns.

Wider trenches are bombarded with ions with higher energies (more intensive etching?).

- 250 µm
- 100 µm
- 50 µm
- 20 µm
REMOTE PLASMA TREATMENT OF BACTERIA CONTAMINATED ROUGH SURFACES
Discharge is confined by electrodes and quartz slides at the sides of the jet.

- 13.56 MHz, 1 atm, He/O₂/H₂O = 95/4.5/0.5, 1000 SCCM
- A high flow rate produces a jet of reactive species.
- Shroud of air surrounds jet with entrainment.
- Rough surface (5-10 µm) with bacteria (a few µm).

T. Gans, Queens Univ. Belfast
V. Schulz von der Gathen, Ruhr-University Bochum
PLASMA PARAMETERS

- Potential (-300 to 300 V)

- Te (0.2 – 3 eV)
  - Electron Temperature (0-3 eV)

- E/N (0 – 150 Td)
  - E/N (0-150 Td)

- [e] $1.4 \times 10^{12}$ (2dec)
  - Electron Density ($1.4 \times 10^{12}$ cm$^{-3}$)

- RF discharge, 13.56 MHz, 1 atm, He/O$_2$/H$_2$O = 95/4.5/0.5
- $T_e$ = 2-3 eV is typical for atmospheric pressure discharges.
- High E/N in the sheath regions as in typical RF discharges.
- Electron density of $10^{12}$ cm$^{-3}$ in close agreement to experiment.
Impingement of jet onto surface produces somewhat turbulent conditions.

N₂ from room air is entrained into jet, thereby enabling reaction with plasma excited species.

- He with fluid streamlines
- N₂

- 20-65 ms
- 1 atm, He/O₂/H₂O = 98.5/0.5, 1000 sccm
OH DENSITY, FLUXES

- **He/O₂ = 98/2**
- **He/O₂ = 99.8/0.2**

- 20-65 ms
- 1000 sccm

**Linear Scale**

- OH production is inversely proportional to oxygen content.

**Bacteria Number**

<table>
<thead>
<tr>
<th>0.2% O₂</th>
<th>2% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
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</tbody>
</table>

**OH radicals**

- Radial Fluxes (10¹⁵ cm⁻² s⁻¹)

**Radical Fluxes (10¹⁵ cm⁻² s⁻¹)**

- Position Along Surface With Roughness (µm)

**OH Radicals**

- **Log scale**

**MIN**

**MAX**
There are two groups of radicals.

$O_2(^1\Delta)$ and atomic oxygen scale linearly with the oxygen content.

NO, OH, O$_3$ scale inversely proportional to the oxygen content.

As these ROS are long lived (for these conditions), they accumulate as gas passes through plasma zone.

1 atm, He/O$_2$/H$_2$O = 98.5/0.5, 1000 sccm
Atomic O fluxes scale with O₂ content but are generally small compared to other ROS and NO.

Increasing flow rate can make significant increase in fluxes due to reduced reaction time.
CONCLUDING REMARKS

- Many challenges in plasma medicine and in modeling of plasma medicine.
- Many, many unknowns in specifics of plasma generated species reacting with living tissue.
- With this complexity, what insights can you expect from the modeling?
  - Tissue is not passive during the plasma treatment. Shape and dielectric properties of the wound matter – *How might strategies to account for these interactions be implemented?*
  
- The cause and effect (RNS incident onto a wound leading to wound healing) has many, many steps between – *Candidate reaction mechanisms should be tested and refined.***

- Bacteria and virus are rarely in convenient locations to be killed – *Strategies for plasma to reach bacteria in nooks-and-crannies.*

- All reactive fluxes are likely important but not all reactive fluxes have equal opportunities to interact with target – *What are relative contributions of radicals, ions, photons?*
PLASMA MEDICINE: ROADMAP

- **Experimental**
  - Different mechanisms: bacteria, mammalian cells, tissues.
  - Electric fields: Electroporation of cell membrane and drug delivery at the molecular level
  - ROS, plasma ions, UV: Catalysis and triggering biological responses
  - Selectivity: tissue sterilization without damage, apoptosis in cancer cells
  - Intensity: Low: Sterilization, Coagulation; Intermediate: cell proliferation; High: normal cell death; Very high: necrosis

- **Computational**
  - Plasma sources relevant to plasma medicine – optimization.
  - Databases of relevant ambient chemistries: collection and validation
  - Prediction of electric fields over cell membranes
  - Quantitative classification and optimization of fluxes: ions, ROS, RNS, UV
  - Study of interdependencies. Demonstration of the ability to penetrate into small pores and microscopic openings.

With this complexity and interdependencies, computer modeling of plasma-tissue interactions increases predictive capabilities for plasma medicine.