Introduction
Introduction

The graph shows the electric field ($10^8$ V/m) over time (fs). The electric field peaks at around 20 fs and oscillates with a frequency that is not explicitly shown on the graph.
Introduction
Introduction

[Diagram showing wave patterns with labels: high intensity, normal index, low intensity, higher index]
Introduction

- High intensity
- Normal index
- Low intensity
- Higher index

Diagram showing a waveform with arrows indicating direction and labels for high and low intensity.
Introduction

- High intensity
  - Higher index
- Low intensity
  - Normal index
Introduction

"self phase modulation"
Introduction
Introduction
1. INTRODUCTION

The interaction of intense femtosecond laser pulses with solids offers the possibility of producing a new class of plasmas having approximately solid-state density and extremely sharp density gradients. These high-density plasmas with exponential density scale lengths much smaller than the wavelength of light are currently of great interest. Electric breakdown of dielectrics, that is, rapid ionization and formation of a plasma when the material is exposed to electric fields exceeding some critical value, is a rather general phenomenon. It has been investigated for a wide variety of different situations ranging from static-electrical breakdown to very-high-frequency laser fields. One of the key points in the research of Bloembergen and his co-workers was the use of very tightly focused laser beams, which allowed them to reach the breakdown thresholds of the materials while staying well below the critical power of self-focusing. Self-focusing is one of the major problems in the measurement of bulk breakdown thresholds. In a more recent review Soileau et al. carefully examined the role of self-focusing in experiments measuring laser-induced breakdown of bulk dielectric materials. They concluded that the breakdown and damage thresholds are also strongly influenced by extrinsic effects.

Thus far, the issue of breakdown thresholds in femtosecond laser–solid interaction has barely been touched. Very recently, Du et al. carried out laser-induced breakdown experiments on fused silica with pulses ranging in duration from 7 ns to as low as 150 fs. They reported an interesting dependence of the fluence threshold on the pulse duration, particularly a pronounced increase of the threshold with decreasing pulse duration below 10 ps.

In this paper we describe measurements of the breakdown and plasma formation thresholds. In experiments on fused silica with pulses ranging in duration from 7 ns to as low as 150 fs. They reported an interesting dependence of the fluence threshold on the pulse duration, particularly a pronounced increase of the threshold with decreasing pulse duration below 10 ps.

One of the key points in the research of Bloembergen and his co-workers was the use of very tightly focused laser beams, which allowed them to reach the breakdown thresholds of the materials while staying well below the critical power of self-focusing. Self-focusing is one of the major problems in the measurement of bulk breakdown thresholds. In a more recent review Soileau et al. carefully examined the role of self-focusing in experiments measuring laser-induced breakdown of bulk dielectric materials. They concluded that the breakdown and damage thresholds are also strongly influenced by extrinsic effects.
Introduction


“... clear evidence that no bulk plasmas...

[and] ... no bulk damage could be produced with femtosecond laser pulses”
Introduction

focus laser beam inside material

Introduction
Outline

• Femtosecond materials interactions
• subcellular surgery
• nanoneurosurgery
Femtosecond materials interactions

focus laser beam inside material

Femtosecond materials interactions

high intensity at focus...

100 fs

objective

transparent material
Femtosecond materials interactions

...causes nonlinear ionization...
and ‘microexplosion’ causes microscopic damage…

Femtosecond materials interactions
Femtosecond materials interactions

photons energy $< \text{bandgap} \rightarrow \text{nonlinear interaction}$
Femtosecond materials interactions

nonlinear interaction provides bulk confinement
Femtosecond materials interactions

nonlinear interaction provides bulk confinement
Femtosecond materials interactions

SEM & AFM:

- 100-nm cavities
- little collateral damage
Femtosecond materials interactions

Dark-field scattering

objective

sample
Femtosecond materials interactions

block probe beam...
Femtosecond materials interactions

... bring in pump beam...
Femtosecond materials interactions

... damage scatters probe beam
Femtosecond materials interactions

scattered signal

![Graph showing scattered signal over time (µs) for fused silica with an input of 0.1 µJ.](image)
Femtosecond materials interactions

scattered signal

signal (a.u.)

fused silica
1.0 µJ

time (µs)
Femtosecond materials interactions

scattered signal

![Graph showing scattered signal over time](image)

- **Signal (a.u.)**
- **Time (µs)**

- **Fused silica**
  - Energy: 1.0 µJ

**Plasma**

The graph illustrates the scattered signal over time for fused silica with a pulse energy of 1.0 µJ. The signal peaks at approximately 0.2 µs.
Femtosecond materials interactions

scattered signal

![Graph showing scattered signal for fused silica with 1.0 µJ energy, indicating a peak signal and a permanent change over time (µs)].
Femtosecond materials interactions

scattered signal

![Graph showing the scattered signal over time for fused silica with a thermal transient at 1.0 µJ.]
Femtosecond materials interactions vary numerical aperture

**intensity threshold:**

\[ E_{th} = I_{th} \tau A \]

**spot size determined by numerical aperture:**

\[ E_{th} = I_{th} \tau \lambda^2 \frac{1}{\pi (NA)^2} \]
fit gives threshold intensity: $I_{th} = 2.5 \times 10^{17} \text{ W/m}^2$
Femtosecond materials interactions

vary material...

![Graph showing threshold intensity (10^17 W/m^2) vs. bandgap (eV) for different materials including LiF, CaF_2, FS0211, BK7, SF11, and 2124 8 106.](image)
Femtosecond materials interactions

...threshold varies with band gap (but not much!)

<table>
<thead>
<tr>
<th>Bandgap (eV)</th>
<th>Threshold Intensity (10^{17} W/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
</tr>
<tr>
<td>5</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>4.0</td>
</tr>
<tr>
<td>7</td>
<td>4.5</td>
</tr>
</tbody>
</table>

- LiF
- CaF$_2$
- FS
- SF11
- 0211
- BK7
- SF11
Femtosecond materials interactions

- nonlinear interaction
- disrupt matter inside bulk
- ablation at very low energy
Outline

- femtosecond materials interactions
- subcellular surgery
- nanoneurosurgery
Q: can we ablate material on the subcellular scale?
Subcellular surgery

Requirements:

- submicrometer precision (in bulk)
- no damage to neighboring structures
- independent of structure/organelle type
Subcellular surgery

Cytoskeleton

- gives a cell its shape
- provides a scaffold for organelles
- responsible cell motion and attachment
- facilitates intracellular transport and signaling
- required for cell division
Subcellular surgery

two components

actin fibers

microtubules
Subcellular surgery

epi-fluorescence microscope

UV lamp

objective

CCD camera
Subcellular surgery

- UV lamp
- Objective
- CCD camera

fluorescently label sample
Subcellular surgery

UV illumination...
Subcellular surgery

...causes fluorescence
Subcellular surgery

Irradiate with fs laser beam
Subcellular surgery

UV lamp → sample → objective → fluorescence → CCD camera

examine resulting ablation
Subcellular surgery
Subcellular surgery
Subcellular surgery

nucleus of fixed endothelial cell

white light microscopy
Subcellular surgery

nucleus of fixed endothelial cell

fluorescence microscopy
Subcellular surgery

irradiate with fs laser

fluorescence microscopy
Subcellular surgery

irradiate with fs laser

fluorescence microscopy
Subcellular surgery

bleaching or ablation?

TEM image
Subcellular surgery

three regions of interaction

![Graph showing TEM and fluorescence ablation width vs pulse energy](graph.png)
three regions of interaction

Subcellular surgery

- Pulse energy (nJ)
  - 0
  - 1
  - 2
  - 3

- Ablation width (µm)
  - 0
  - 0.4
  - 0.8
  - 1.2

- TEM
- Fluorescence

Graph showing ablation width (µm) against pulse energy (nJ):
Subcellular surgery

three regions of interaction

![Graph showing fluorescence and TEM against pulse energy](image-url)
Subcellular surgery

three regions of interaction

![Graph showing three regions of interaction between pulse energy (nJ) and ablation width (µm). The graph includes TEM and fluorescence data, with a shaded area indicating no damage.]
Subcellular surgery

three regions of interaction

![Graph showing three regions of interaction]

- **pulse energy (nJ)**
  - 0
  - 1
  - 2
  - 3

- **ablation width (µm)**
  - 0
  - 0.4
  - 0.8
  - 1.2

- **No damage**
- **Ablation**

- **TEM**
- **Fluorescence**
Subcellular surgery

three regions of interaction

- Pulse energy (nJ)
  - 0
  - 1
  - 2
  - 3

- Ablation width (µm)
  - 0
  - 0.4
  - 0.8
  - 1.2

- TEM
- Fluorescence

- No damage
- Bleaching
- Ablation
Subcellular surgery

Definitive proof of ablation

- ablation width as small as 100 nm
- ablation threshold varies slightly
- ablation threshold 20% above bleaching threshold
Definitive proof of ablation

- ablation width as small as 100 nm
- ablation threshold varies slightly
- ablation threshold 20% above bleaching threshold
Subcellular surgery

Q: subcellular surgery on live cells?
Subcellular surgery
Subcellular surgery

ethyldium bromide test
Subcellular surgery

ethydium bromide test

target 1
Subcellular surgery

ethydium bromide test
Subcellular surgery

ethyldium bromide test
Q: can we probe the dynamics of the cytoskeleton?
Subcellular surgery

YFP-labeled actin fiber network of a live cell

10 µm
Subcellular surgery

cut a single fiber bundle
Subcellular surgery

cut a single fiber bundle
Subcellular surgery

gap widens with time

10 µm

$t = 10 \text{ s}$
Subcellular surgery

retraction or depolymerization?
Subcellular surgery

retraction or depolymerization?

10 µm
Subcellular surgery

retraction!
dynamics provides information on *in vivo* mechanics

10 µm
overdamped spring: $\Delta L = L_\infty (1 - e^{-t/\tau}) + L_o$
Subcellular surgery

overdamped spring: \[ \Delta L = L_\infty (1 - e^{-t/\tau}) + L_0 \]
$L_0$ and $\tau$ independent of fiber width!
tension in actin filaments is generated by myosin motors
Y27: inhibits some myosin activity
Subcellular surgery

ML7: direct inhibitor of myosin activity

The graph shows the retraction distance (µm) over time (s) for untreated, Y27, and ML7 conditions. The untreated condition shows the least retraction distance, while ML7, which is a direct inhibitor of myosin activity, shows the greatest retraction distance.
Outline

• femtosecond materials interactions
• subcellular surgery
• nanoneurosurgery
Q: can we probe the neurological origins of behavior?
neuron basics

cell body
Nanoneurosurgery

neuron basics

cell body

dendrites
neuron basics
Nanoneurosurgery

neuron basics

![Diagram of a neuron showing cell body, dendrites, and axon.](image)
Nanoneurosurgery

neuron basics

dendrites

cell body

axon
neuron basics
Nanoneurosurgery

neuron basics

dendrites → cell body → axon → to other cells
Nanoneurosurgery

neuron basics

dendrites

cell body

axon
Caenorhabditis elegans

Juergen Berger & Ralph Sommer
Max-Planck Institute for Developmental Biology
Caenorhabditis elegans

- simple model organism
- similarities to higher organisms
- genome fully sequenced
- easy to handle
Nanoneurosurgery

Caenorhabditis elegans

- 80 μm x 1 mm
- about 1000 cells
- 302 neurons
- invariant wiring diagram
- neuronal system completely encodes behavior
Nanoneurosurgery

*Caenorhabditis elegans*
Caenorhabditis elegans
C. elegans life cycle

in utero
C. elegans life cycle
C. elegans life cycle

- in utero
- ex utero
- +2.5 h
- +9 h
- L1
Nanoneurosurgery

C. elegans life cycle

in utero

ex utero

+2.5 h

+9 h

+12 h

L1

L2
Nanoneurosurgery

C. elegans life cycle
Nanoneurosurgery

C. elegans life cycle
C. elegans life cycle

Nanoneurosurgery
C. elegans life cycle

Nanoneurosurgery
Nanoneurosurgery

C. elegans life cycle

- in utero
- ex utero
- adult
- dauer
  - up to 4 months
- L1
- L2
- L3
- L4

+2.5 h
+12 h
+10 h
+8 h
+9 h
+8 h
+8 h
Mapping behavior to neurons

conventional method

worm → mutation → behavioral assay → infer role of neuron
Mapping behavior to neurons

**conventional method**

1. worm
2. mutation
3. behavioral assay
4. infer role of neuron

**femtosecond laser ablation**

1. worm
2. dissect neurons
3. behavioral assay
4. infer role of neuron
ASH neurons

- responsible for chemical sensing
- ciliary projections extend through skin
- one on each side
ASH neurons
ASH neurons
Nanoneurosurgery

ASH neurons
Nanoneurosurgery

ASH neurons

dendrites
axon ring
L/R cell bodies
make ASH neurons express GFP
make ASH neurons express GFP
Nanoneurosurgery

GFP: absorbs UV, emits green
retraction of cut dendrite (6 nJ)
Nanoneurosurgery

retraction of cut dendrite (6 nJ)
retraction of cut dendrite (6 nJ)
Nanoneurosurgery

retraction of cut dendrite (6 nJ)

$t = 3$ min
Nanoneurosurgery

ASH neurons
Nanoneurosurgery

ASK neurons
Nanoneurosurgery

AUA neurons
Nanoneurosurgery

ASI neurons
Nanoneurosurgery

need exquisite precision!
DiO-stained bundle of dendrites
cut single dendrite in bundle (3 nJ)
Nanoneurosurgery

no damage to neighboring dendrites

5 µm
revive worm, reimage 1 day later
Nanoneurosurgery
Nanoneurosurgery

osmolarity assay

glycerol ring
escape rate after ‘mock’ surgery

percent escape vs. time after surgery (h)

0 24 48 72 96

0 20 40 60 80 100
escape rate of ASH-lacking mutant
escape rate after ASH-ablation surgery
Nanoneurosurgery

AFD neurons (temperature sensors)
Nanoneurosurgery
Q: where does the ASH sense temperature?
Nanoneurosurgery

microdroplet assay

glass slide

microdroplet
Nanoneurosurgery

microdroplet assay

glass slide

microdroplet
microdroplet assay

glass slide

microdroplet

video camera
Nanoneurosurgery

surgery results in quantifiable behavior changes
temperature sensing occurs at tip of dendrite
great tool for manipulating the machinery of life
Funding:
Harvard Center for Imaging and Mesoscopic Structures
National Science Foundation
National Natural Science Foundation of China

for a copy of this presentation:
http://mazur.harvard.edu

Follow me! eric_mazur