Computational Biology in the Low Dose Radiation Research Program

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Computer Science
WSU Tri-Cities

Research Areas and Collaborators:

Microbeam Dosimetry: Wilson, Lynch, Lewis, Batdorf

DNA Damage: McAteer, Ernst, Kennedy (PNNL), Dupuis (PNNL)

Cellular Signaling: Zheng, Jin, Springer (PNNL), Resat(PNNL)

For each area: Motivation, Methods, Results

Computational Biology in the Low Dose Radiation Research Program

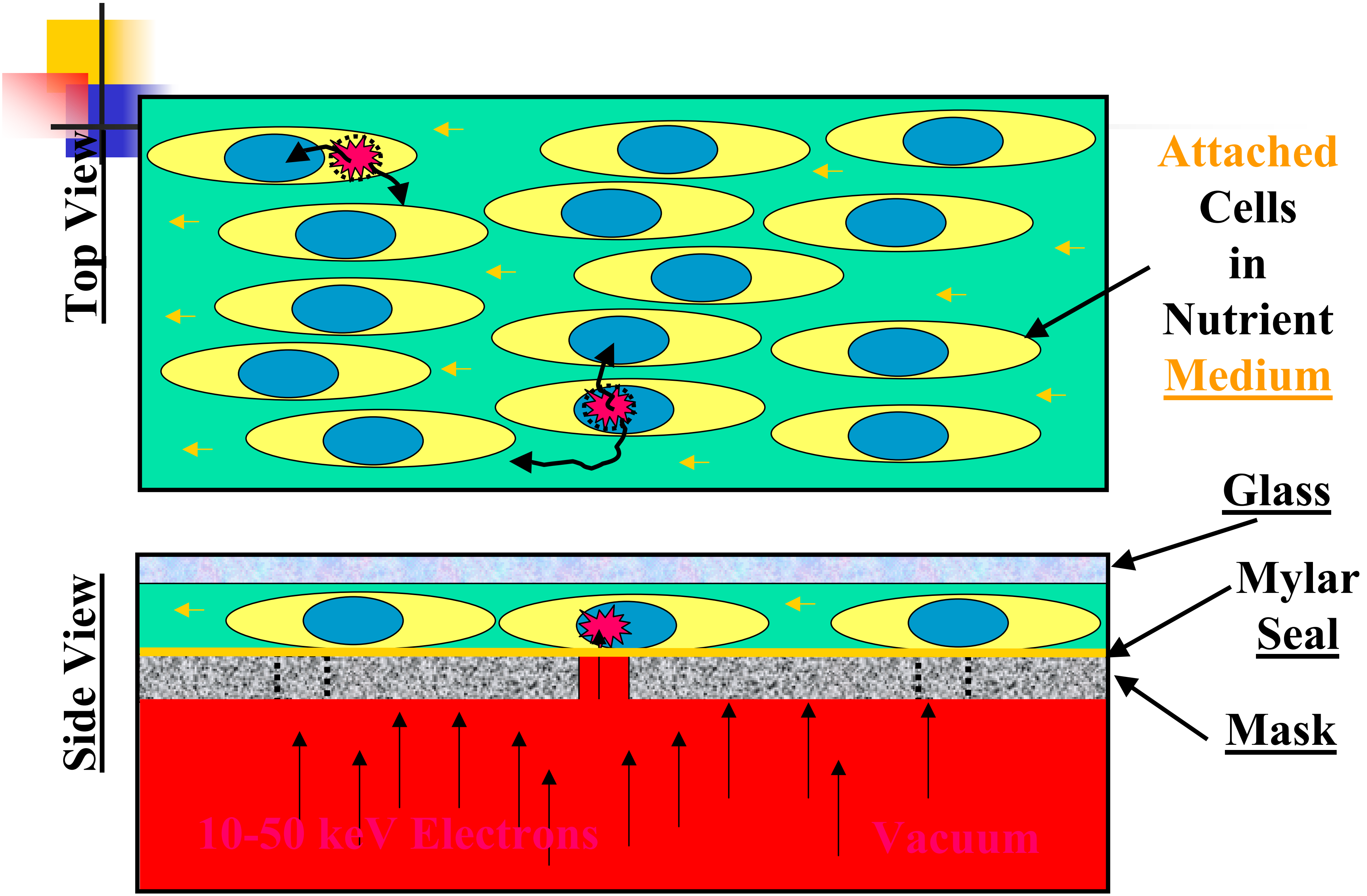
Research Areas:

Microbeam Dosimetry

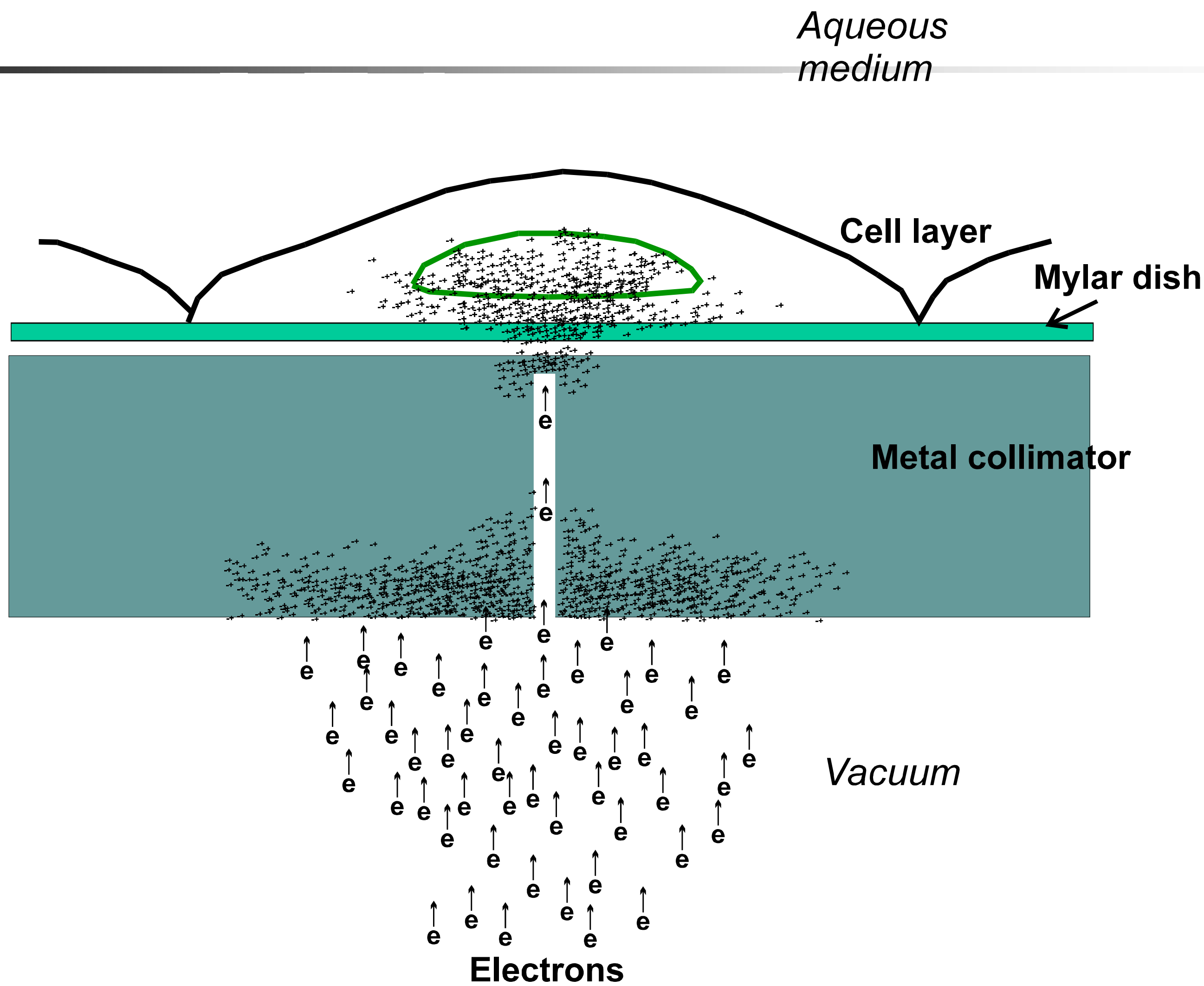
DNA Damage

Cellular Signaling

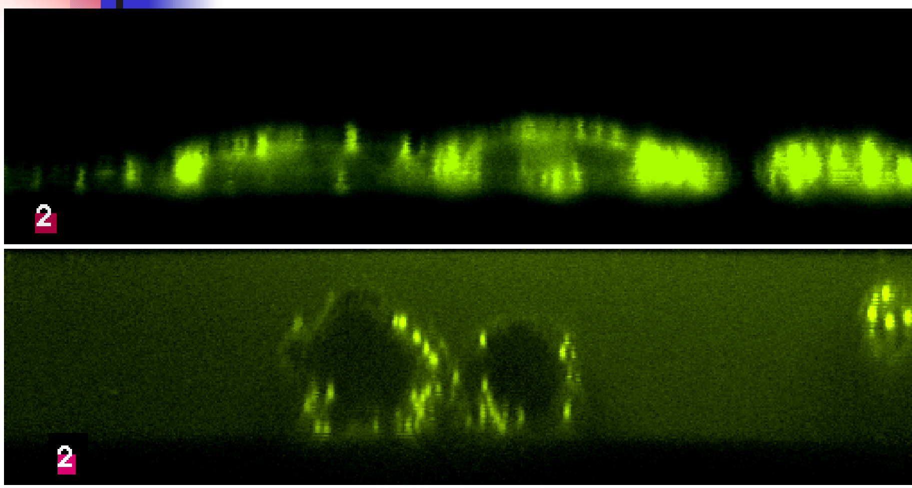
Masked Electron Injection Source For Studying Neighborhood Effects Under Low Dose, Low LET Conditions



Spatially-Resolved Electron Cell Irradiator

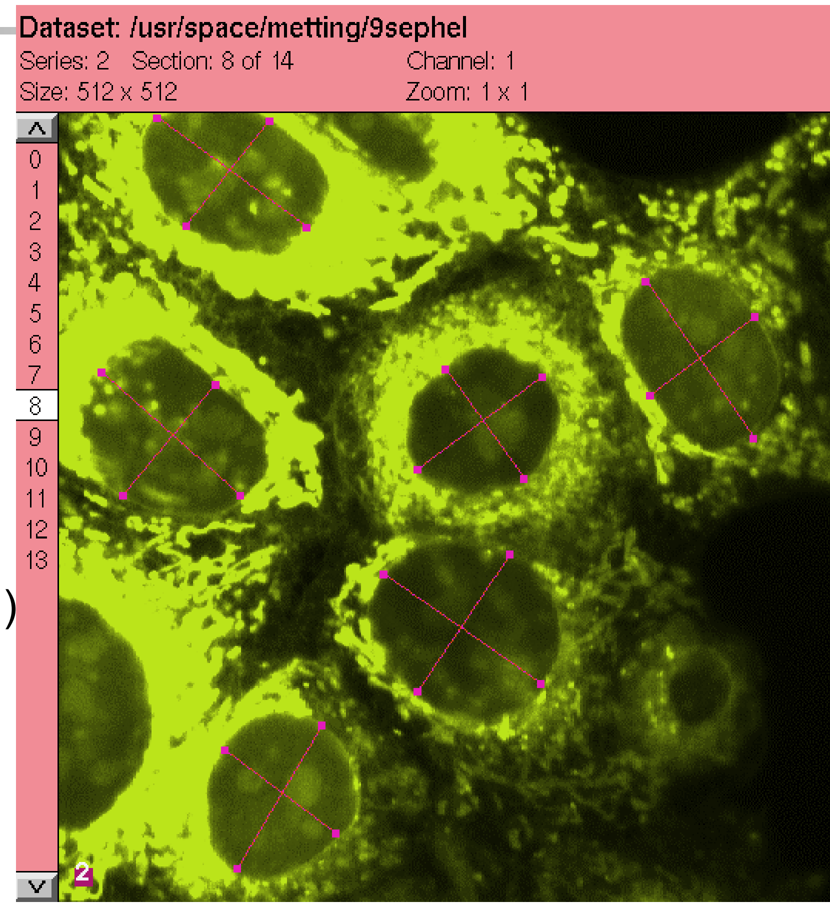


For Model Calculations



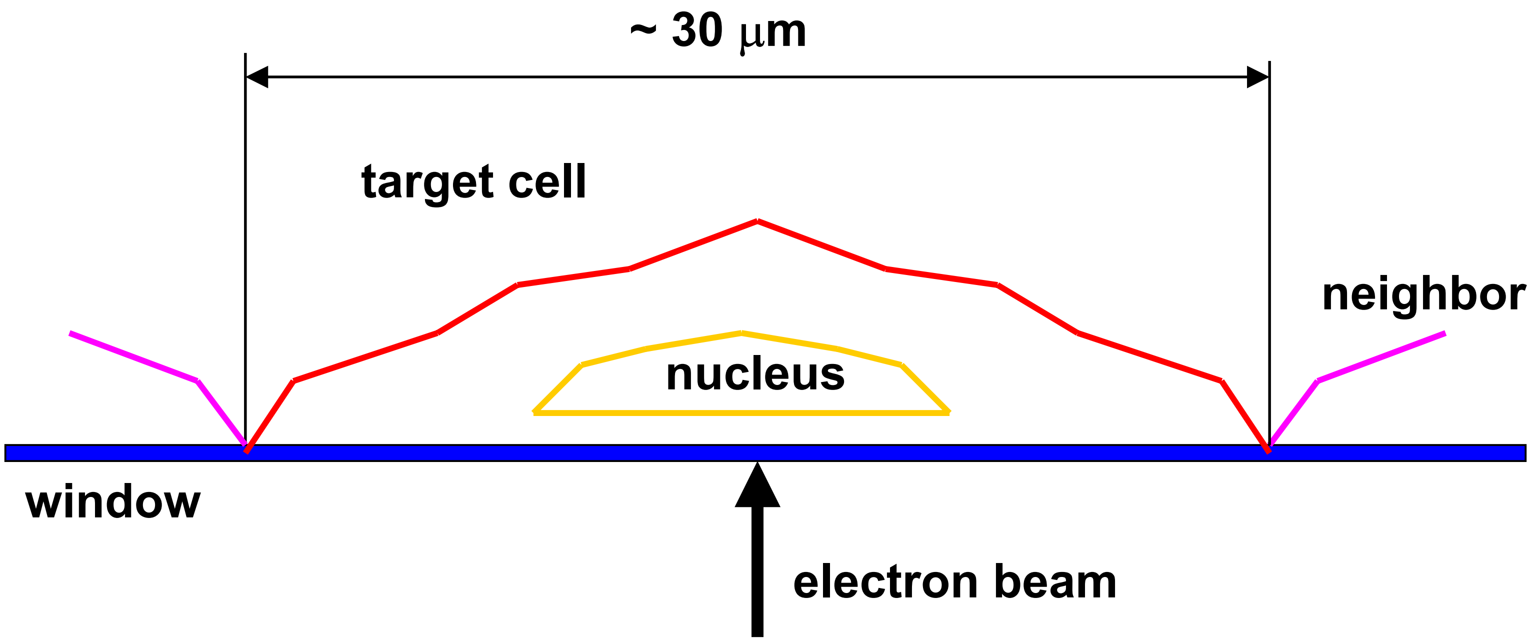
Vertical sections through two cell types, HeLa and mouse macrophage cells, stained to visualize the mitochondria.

(Red boxes are 2 mm on a side.)



Horizontal section of HeLa cells.

Monte Carlo Simulation of Single-cell Irradiation by an Electron Microbeam



Monte Carlo Simulation of Single-cell Irradiation by an Electron Microbeam

<u>Window composition:</u>

Vacuum isolation membrane

- 0.2 μm Si_3N_4

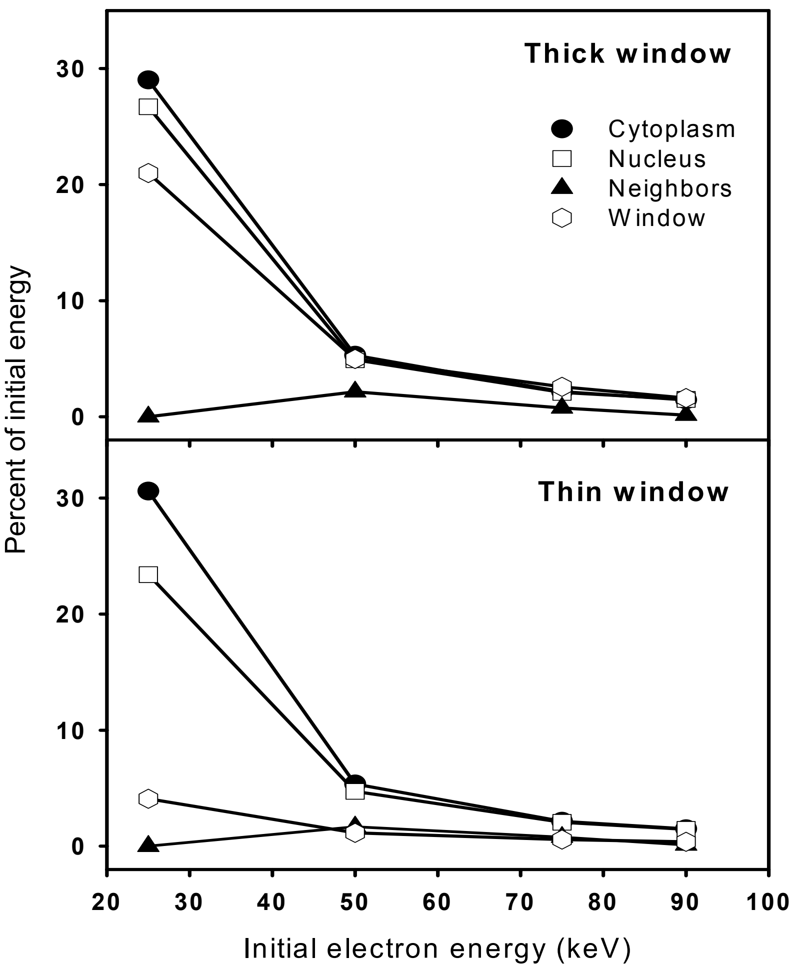
Tissue culture membrane

- 1.5 μm Mylar®

Combined mass per unit area of the two membranes

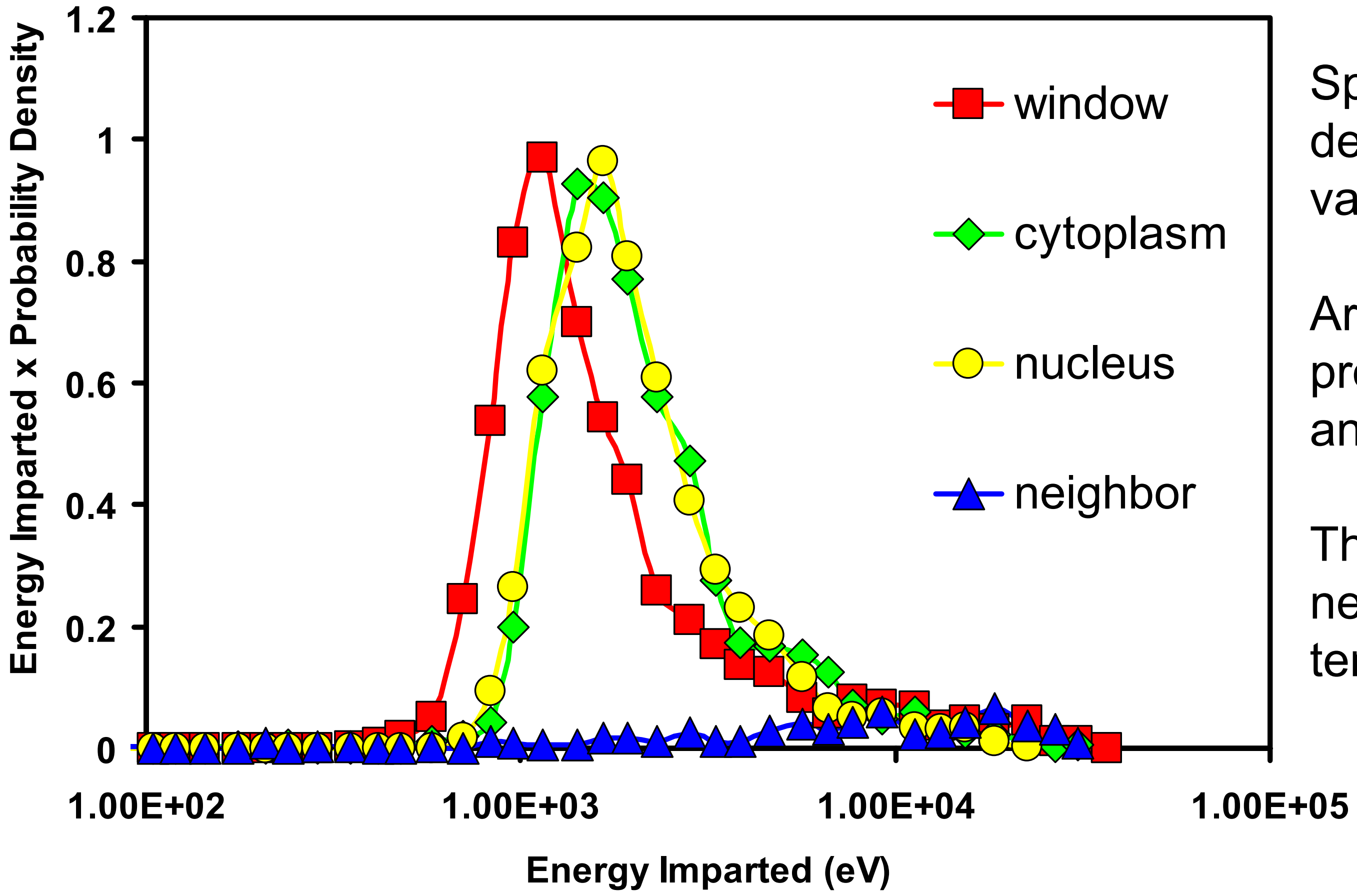
- 0.276 mg/cm^2

Energy (keV)	Neighbors/Target (%)
25	0
50	21
75	18
90	5



Distribution of Event Sizes in Various Cell Compartments

HeLa Cell Irradiation: 50keV electrons



Spectra of energy deposition per track in various cell compartments.

Area under curve is the probability of an event of any size.

The rare events in the neighbor compartment tend to be large.

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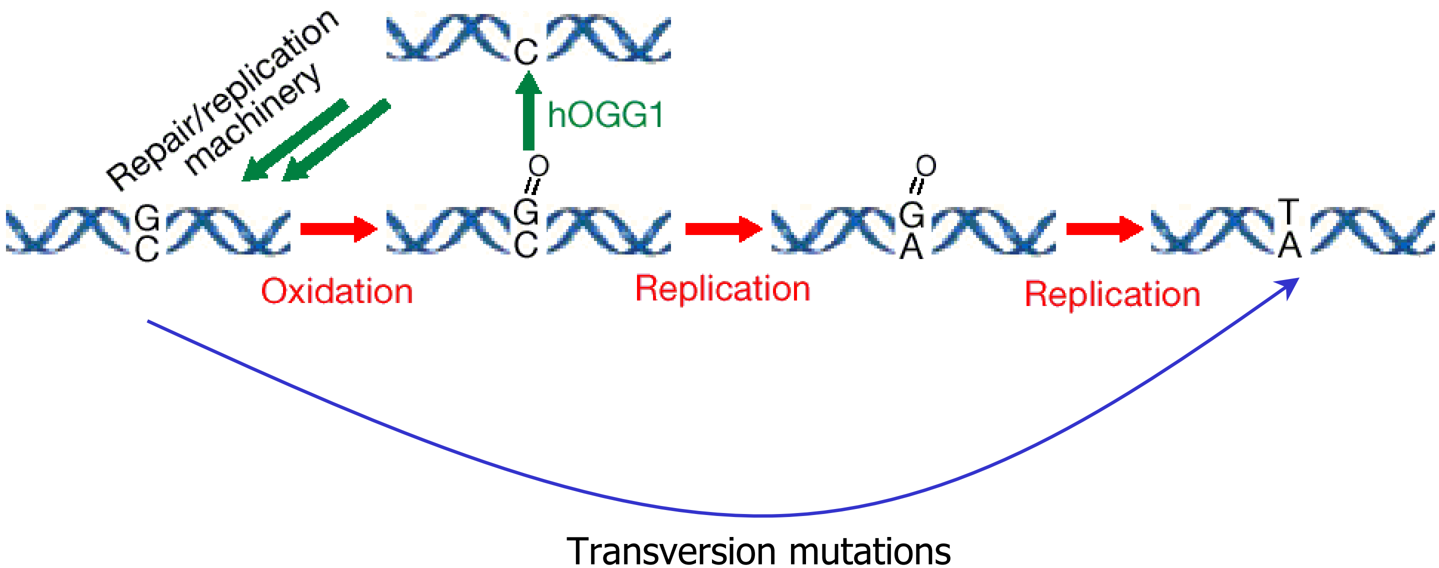
Microbeam Dosimetry

DNA Damage

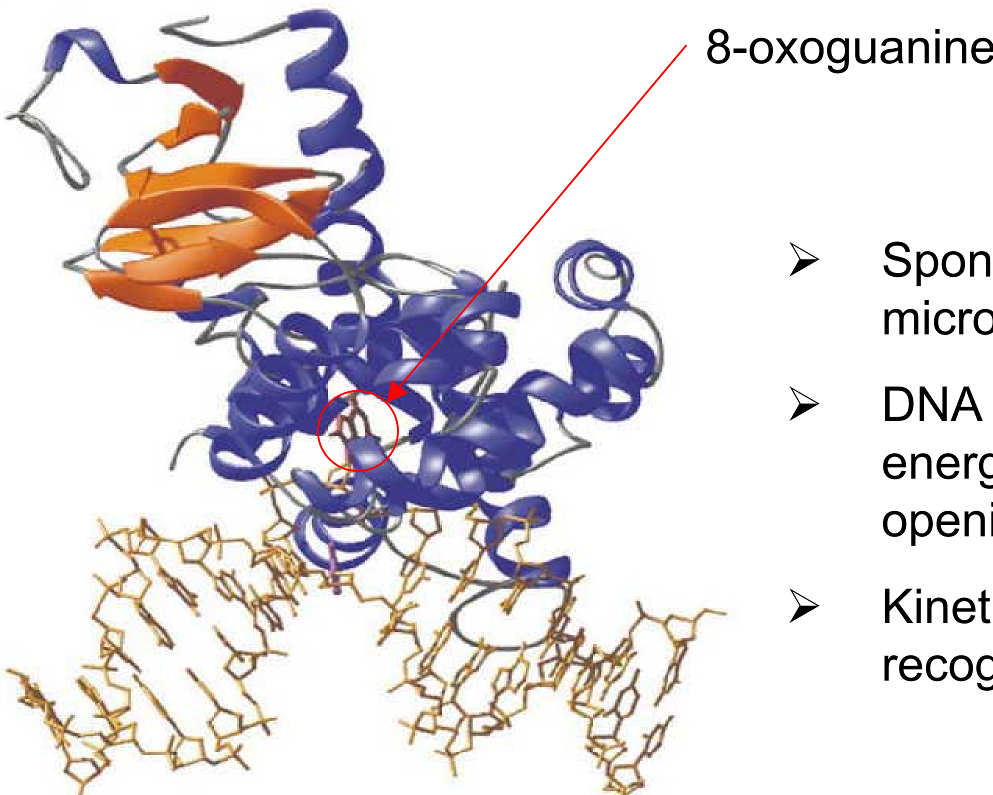
Cellular Signaling

Oxidative Stress and Mutagenesis:



From: Steven Bruner, et al, NATURE, v403, 859-866, 2000

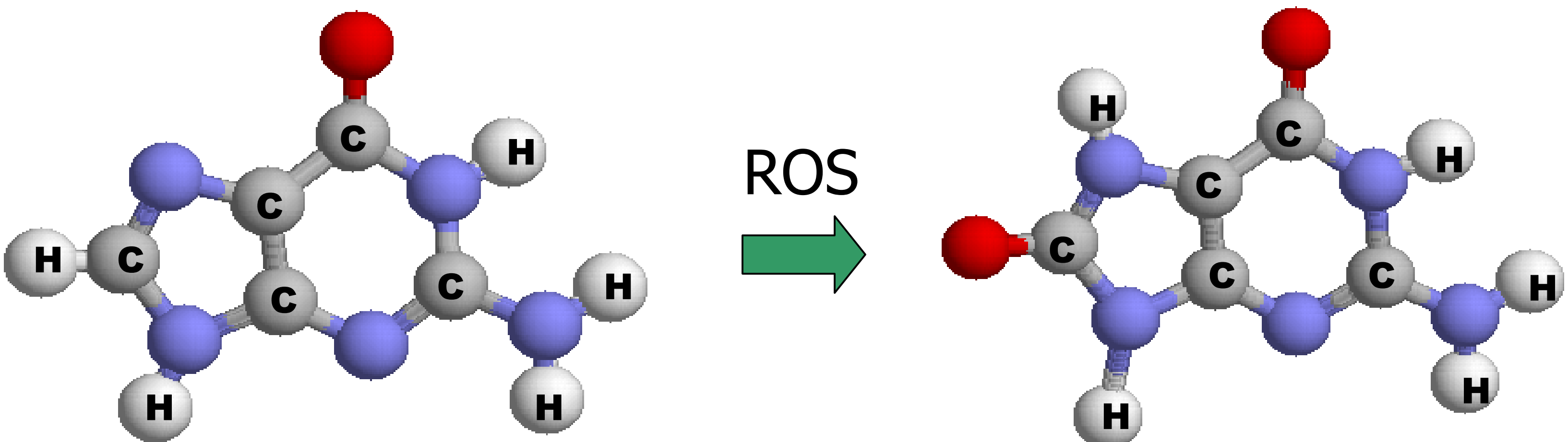
Glycosylase hOGG1 interacting with damaged DNA



- Spontaneous flipping on microsecond time scale.
- DNA bending reduces energy barrier to base opening.
- Kinetic control of damage recognition.

From: Steven Bruner, et al, NATURE, v403, 859-866, 2000

8-hydroxyguanine tautomerization



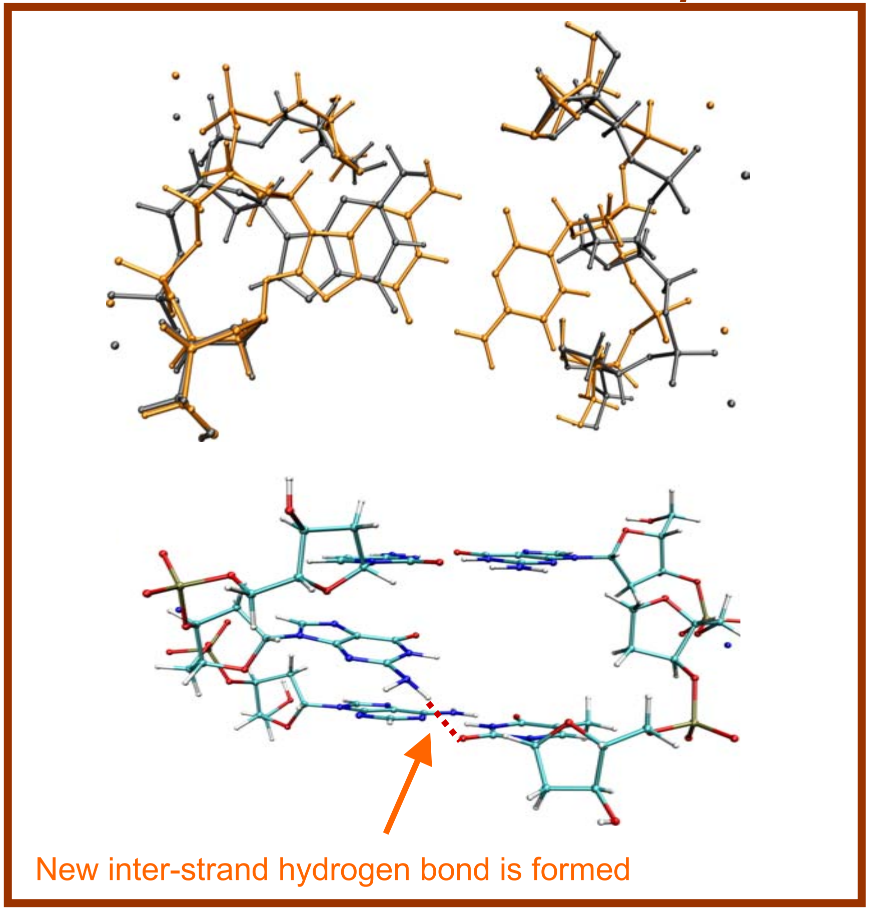
KETO FORM

6.8 - DIKETO FORM

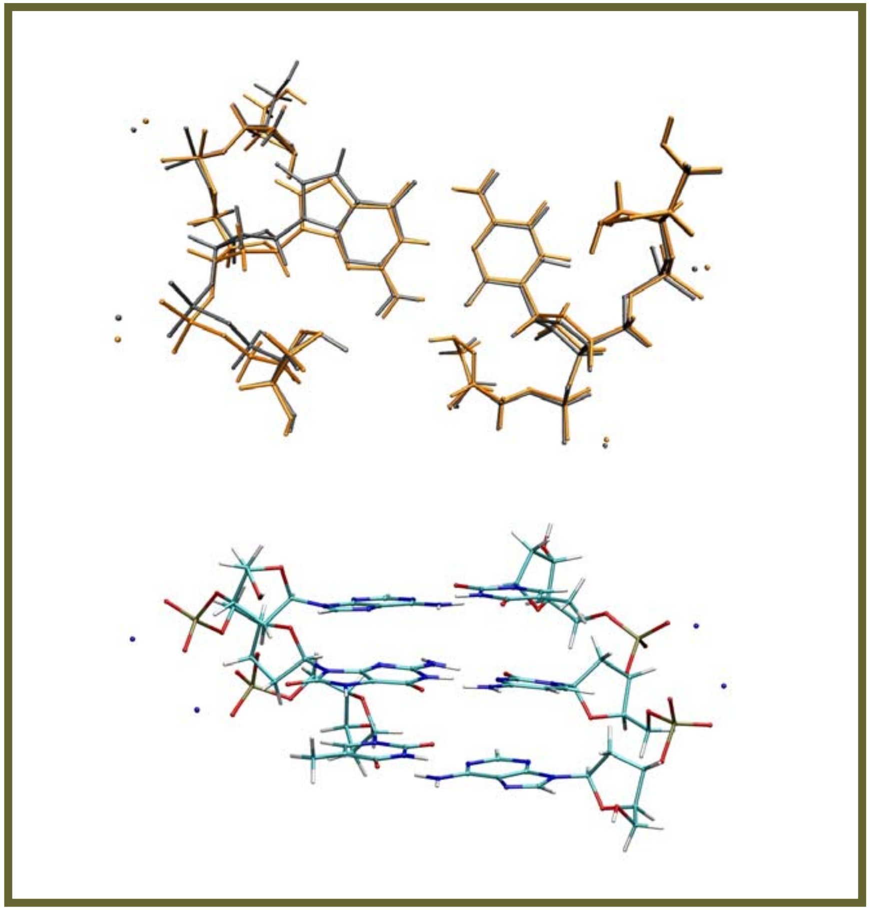
Molecular Energetics of Clustered Damage Sites

Lesion-induced hydrogen-bond energy difference predicted by quantum calculations

Abasic site: ΔE = 15.0 kcal/mol

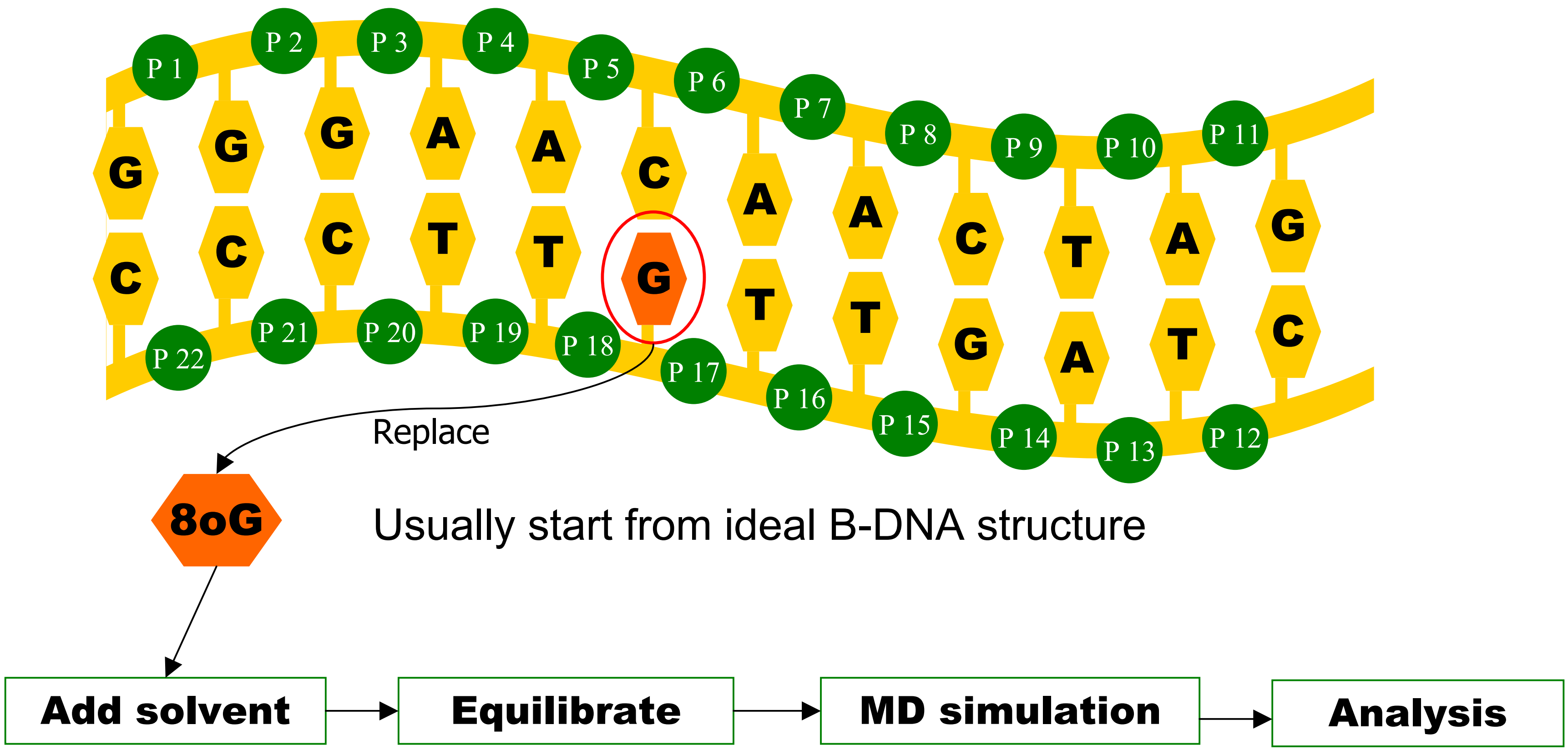


8-oxo-G: ΔE = -2.4 kcal/mol



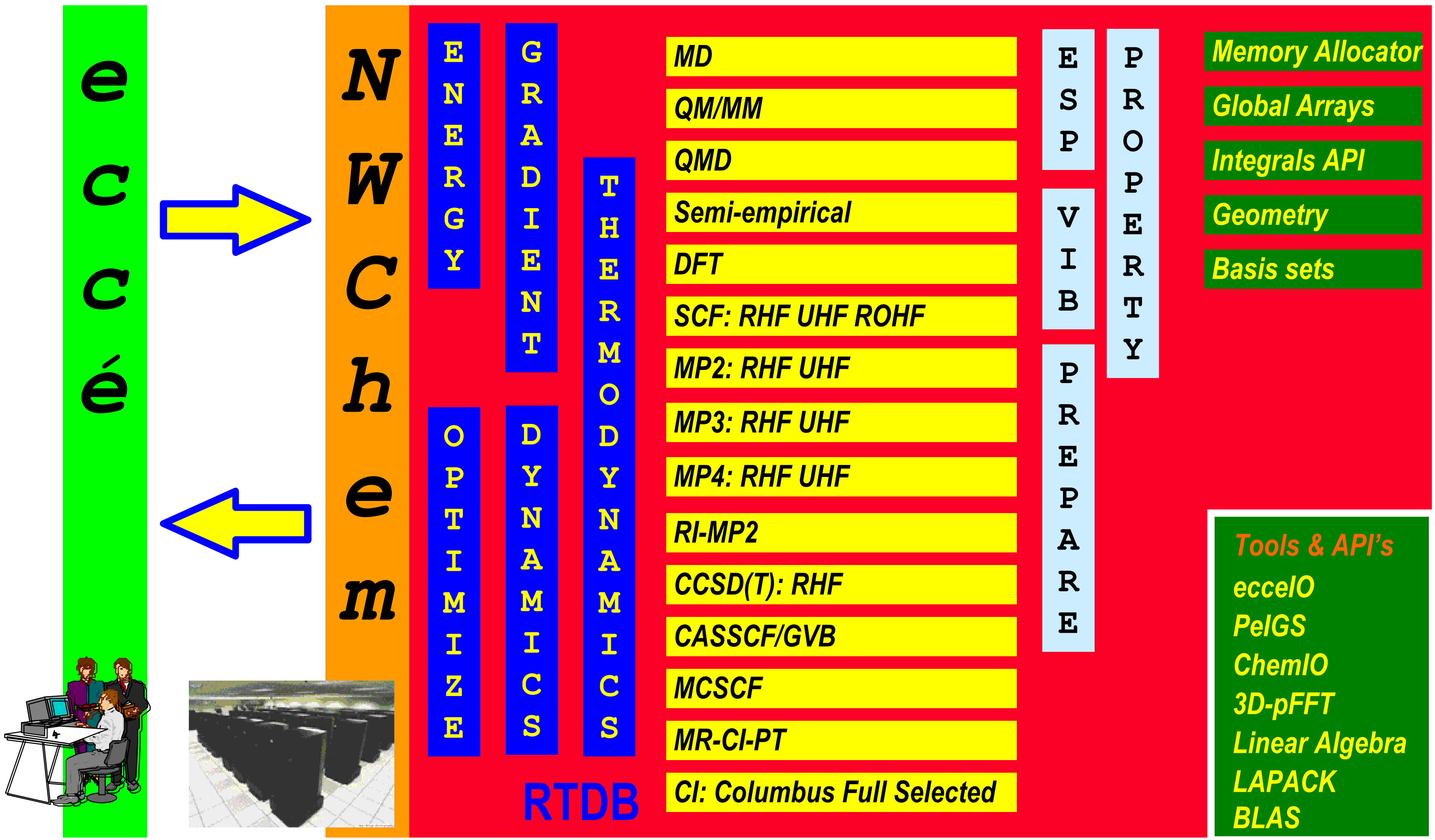
Sequence Context and Starting Structures

Good substrate of Fpg. NMR data available soon.



Usually start from ideal B-DNA structure

NWChem



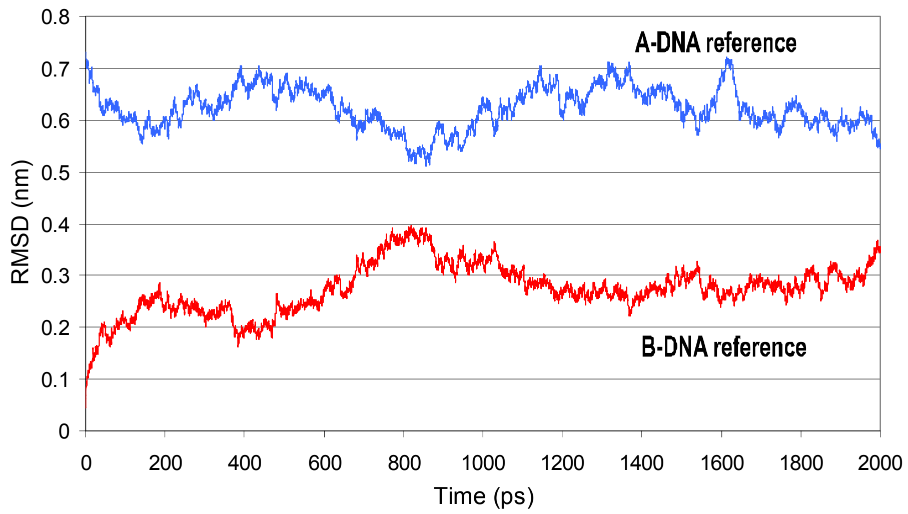
ecce
NWChem
ENERGY
GRADIENT
THERMODYNAMICS
OPTIMIZE
DYNAMICS
MD
QM/MM
QMD
Semi-empirical
DFT
SCF: RHF UHF ROHF
MP2: RHF UHF
MP3: RHF UHF
MP4: RHF UHF
RI-MP2
CCSD(T): RHF
CASSCF/GVB
MCSCF
MR-CI-PT
CI: Columbus Full Selected
RTDB
ESP
VIB
PREPARE
PROPERTY
Memory Allocator
Global Arrays
Integrals API
Geometry
Basis sets
Tools & API's
ecceIO
PeIGS
ChemIO
3D-pFFT
Linear Algebra
LAPACK
BLAS

Analysis of Trajectory Files

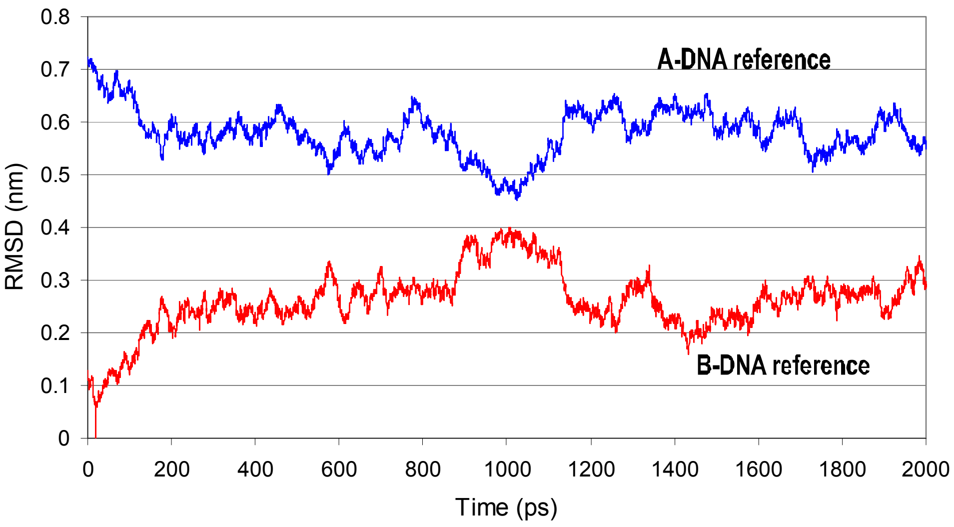
	RMSD	Dials & Windows	Na+ Distance	Bending Analysis	Groove Widths
Native	☑	☑	☑	☑	☑
8oG:C	☑	☑	☑	☑	☑
8oG:A	☑	☐	☑	☐	☐
Flipout	☑	☐	☑	☐	☐

RMSD relative to ideal A- and B-DNA

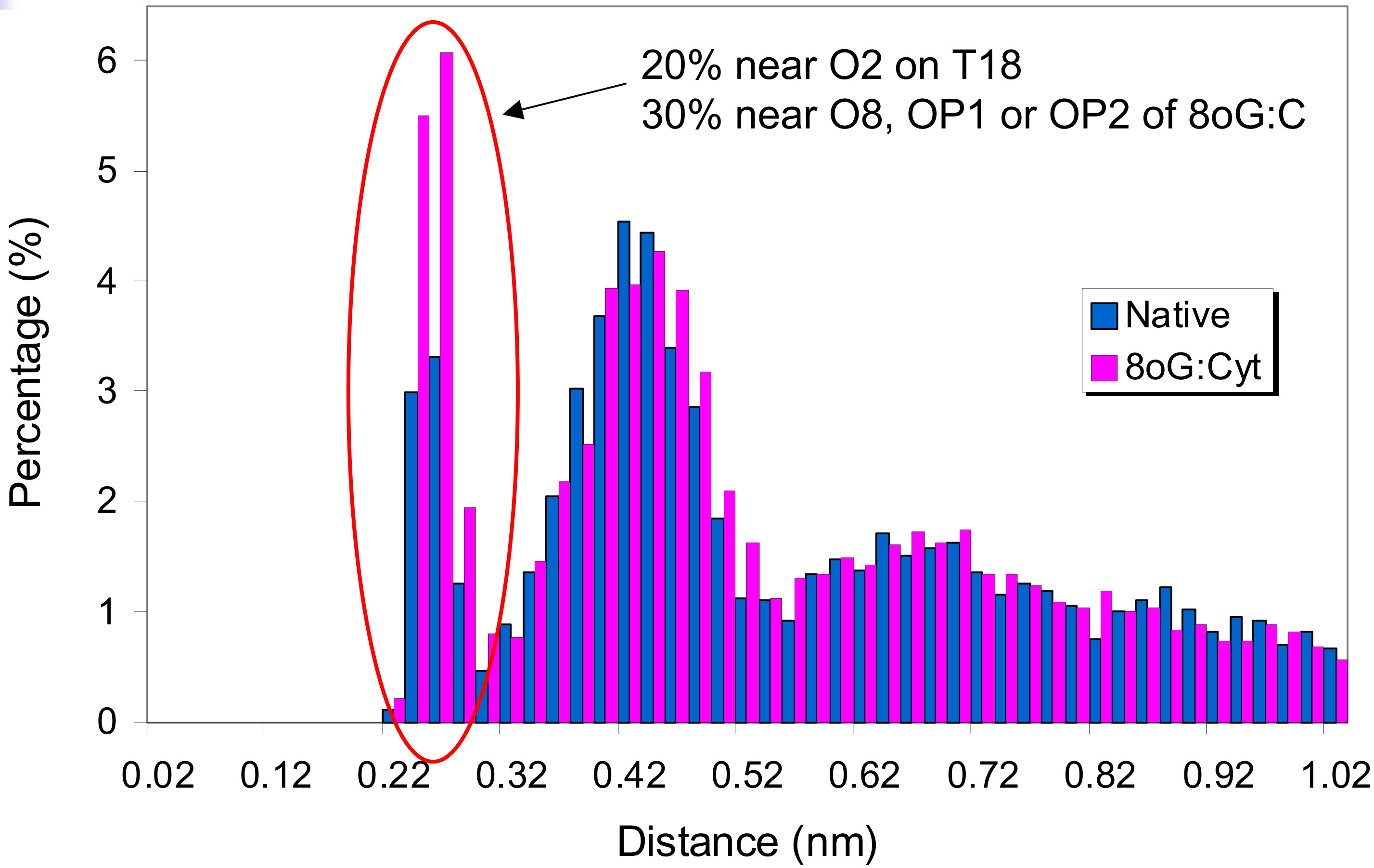
Native



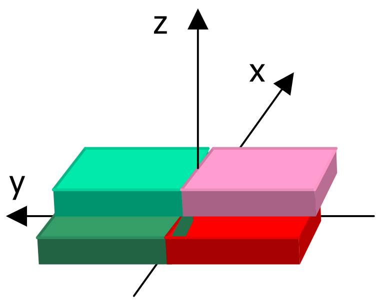
8oG : C



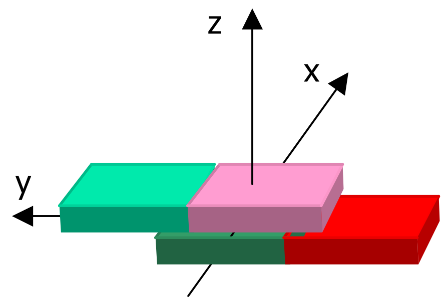
Effect of 8oxoG on distribution of counterions



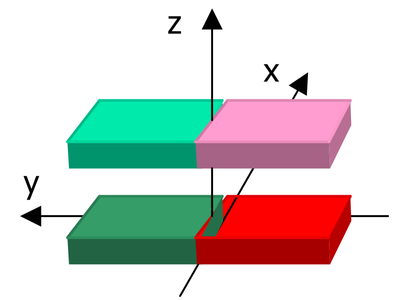
More CURVES parameters



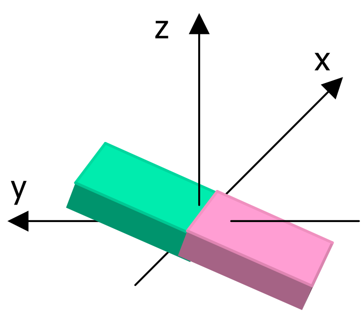
Shift (Dx)



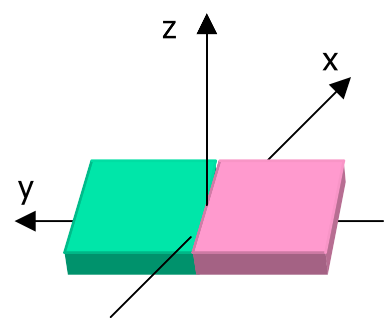
Slide (Dy)



Rise (Dz)

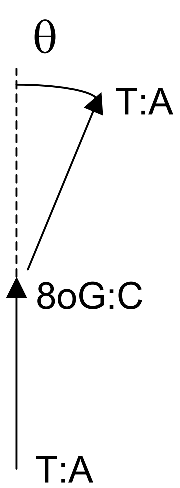


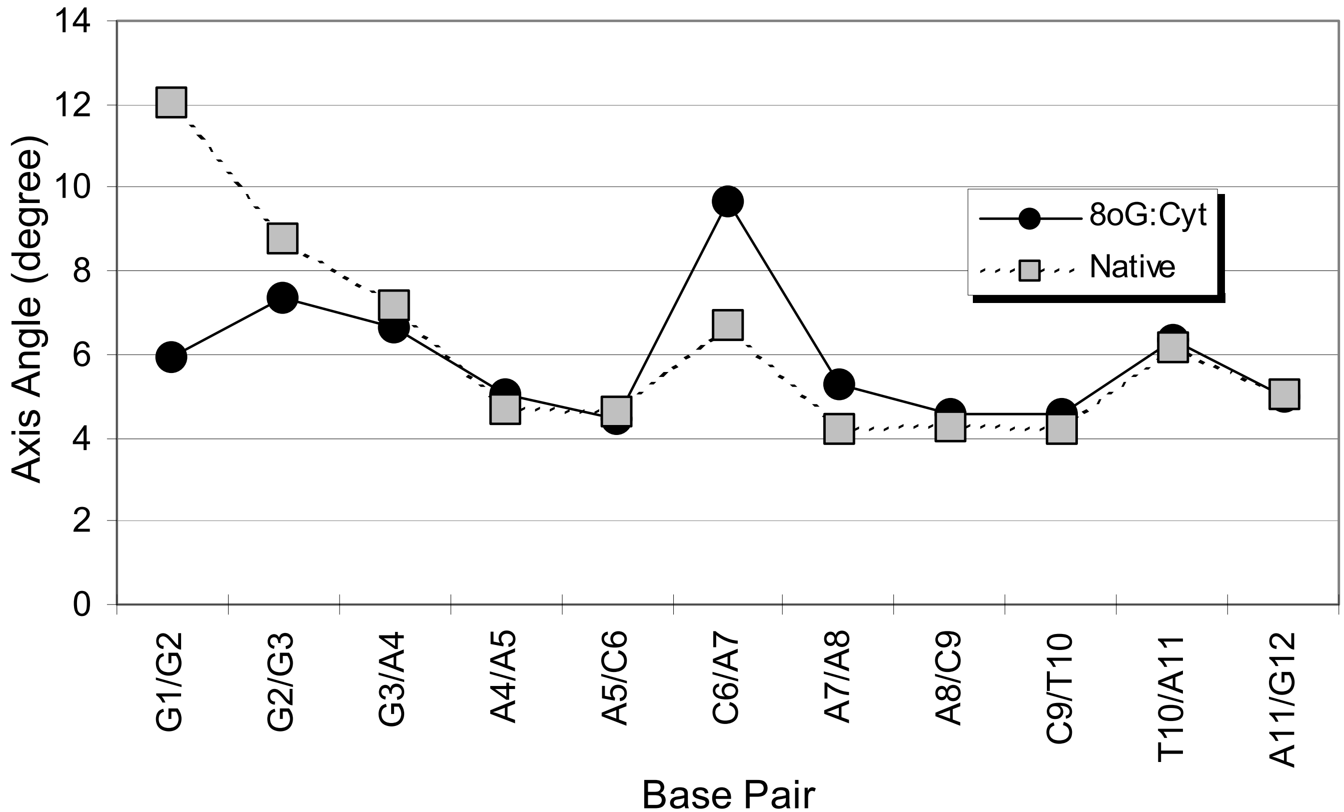
Inclination (η)



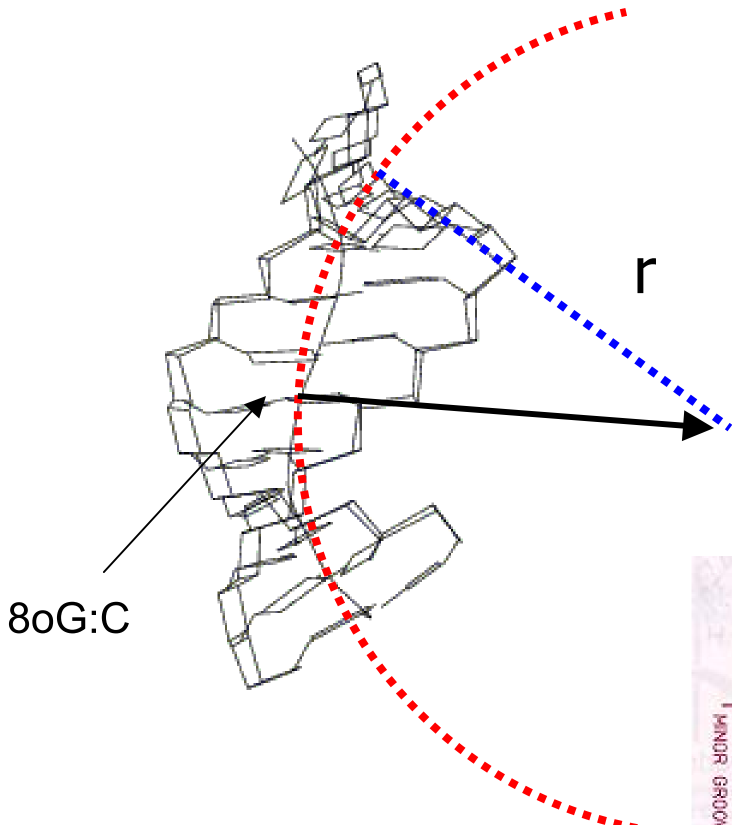
Tip (θ)

Kink at the damage site



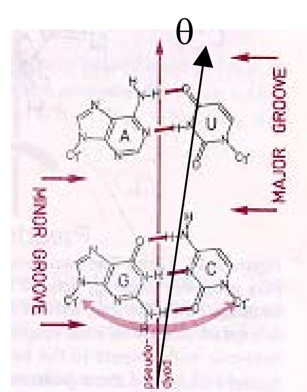


Global bending analysis

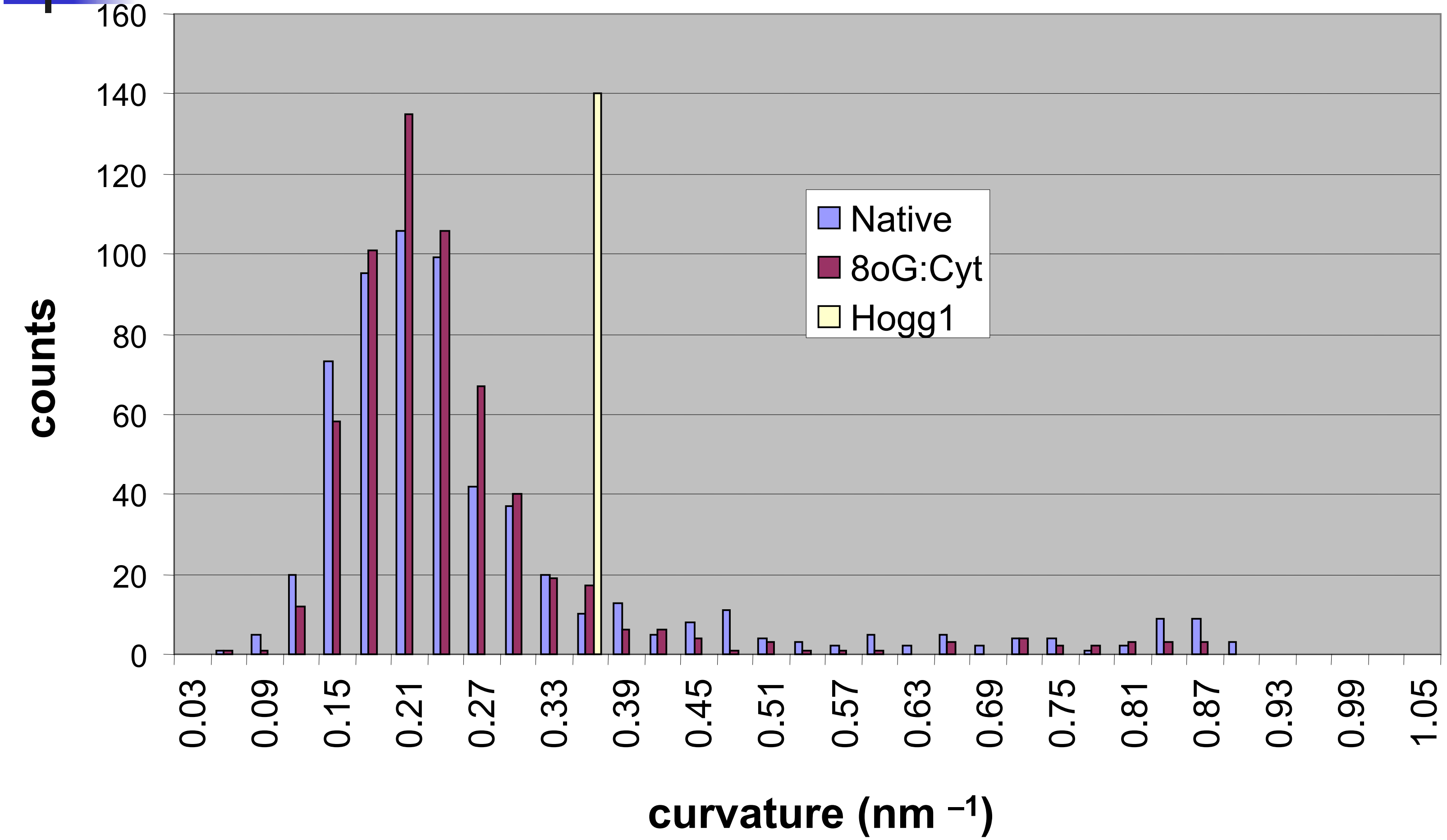


Approach:

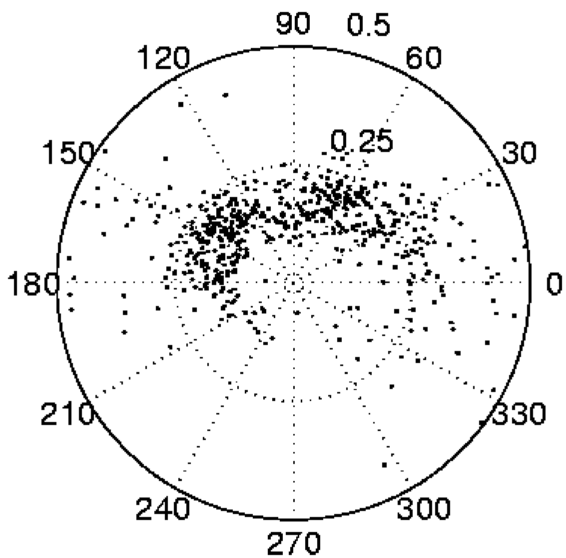
- input CURVES helical axis reference points.
- project helical axis reference points onto plane.
- fit circle to projected points.
- reciprocal of radius is curvature
- connect 8oG:C to center curvature by vector
- project vector onto plane of 8oG:C
- angle between projected vector and pseudo dyad is direction of bending



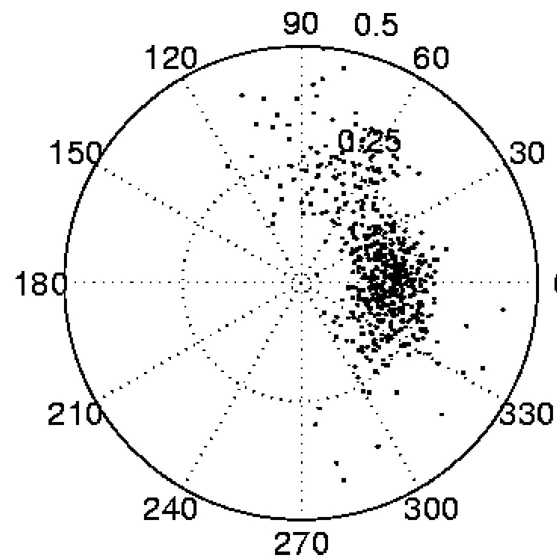
effect of 8oG on bending magnitude



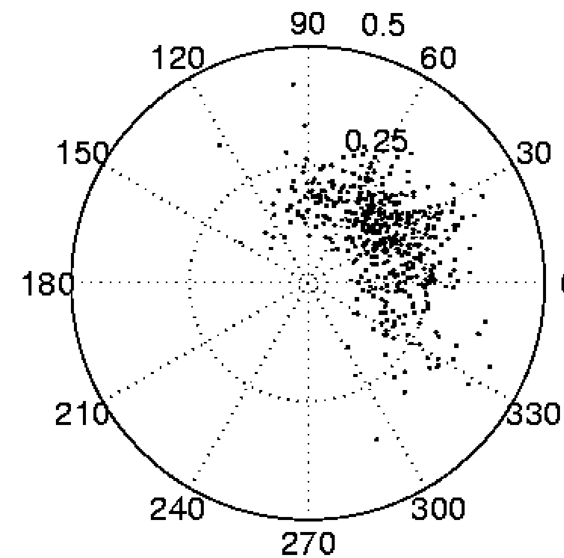
Scatter plots of bending magnitude vs direction



native

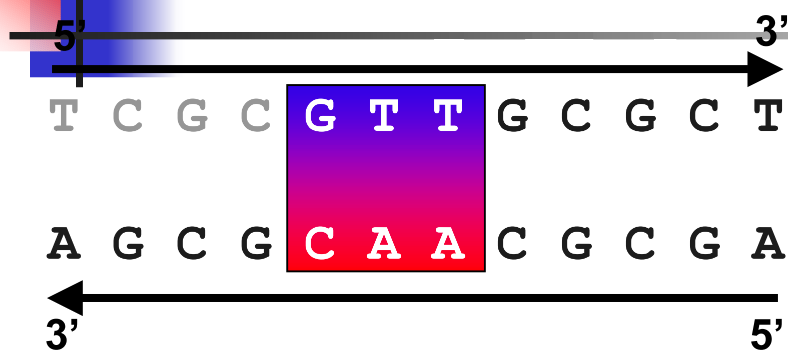


8oG with B-DNA starting structure

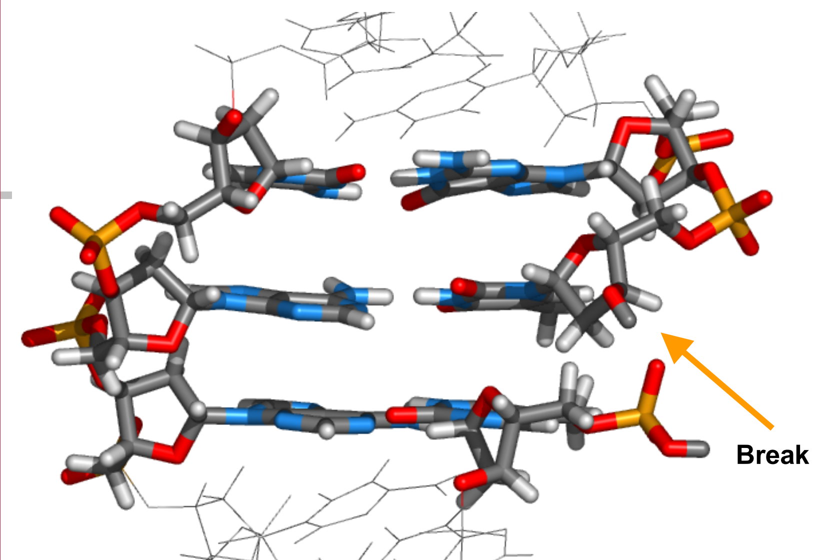


8oG with starting structure bent into minor groove

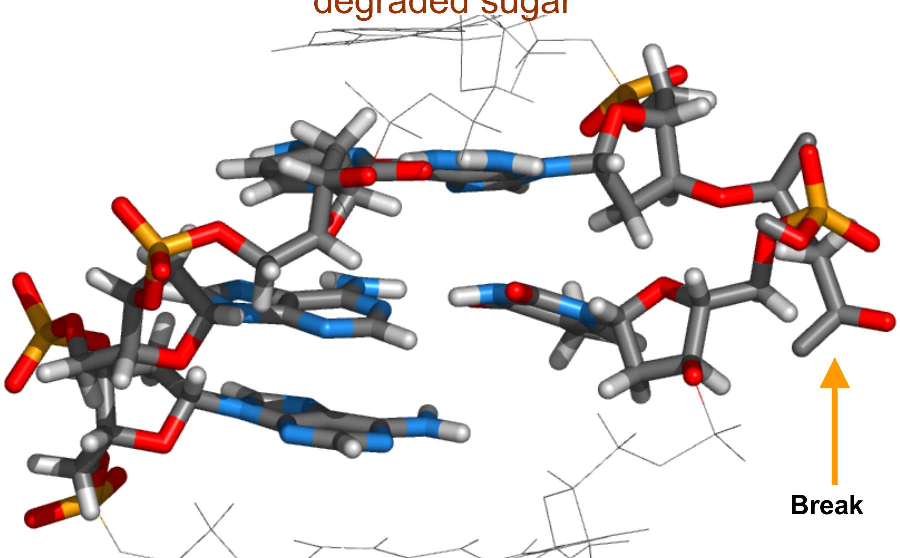
Clustered Damage: Abasic Site and Strand Break



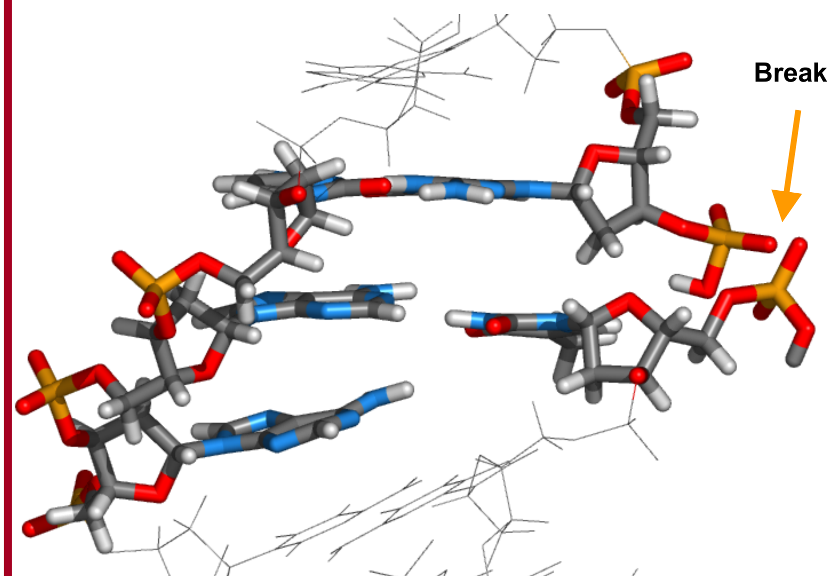
Simple strand break



Strand break with missing base and partially degraded sugar



Strand break with missing base and sugar



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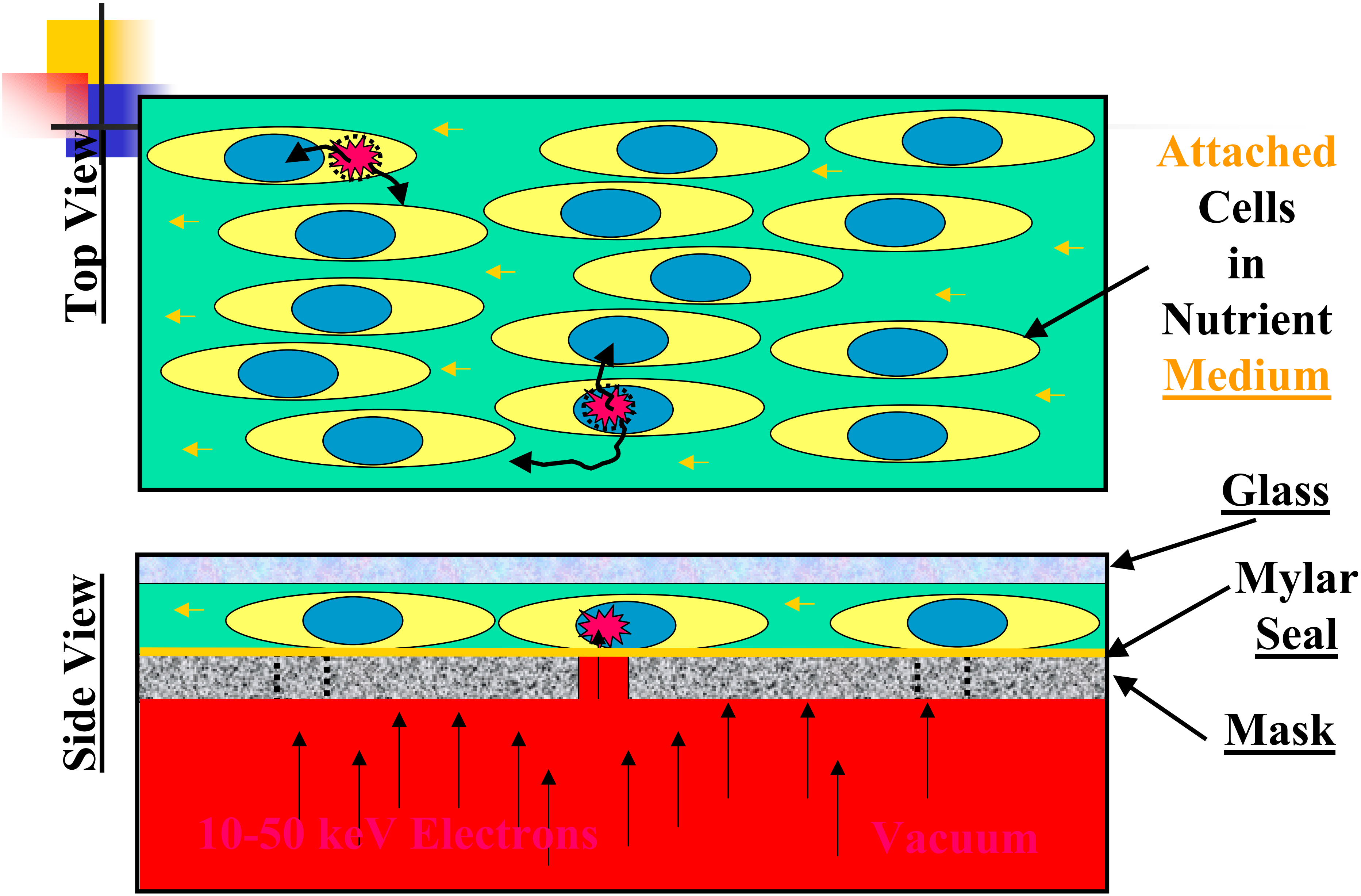
Masked Electron Injection Source For Studying Neighborhood Effects Under Low Dose, Low LET Conditions



Intracellular Calcium Levels in HPV-G Cells After Addition of Medium from Irradiated Cells (Lying, Mothersill and Seymour 2000)

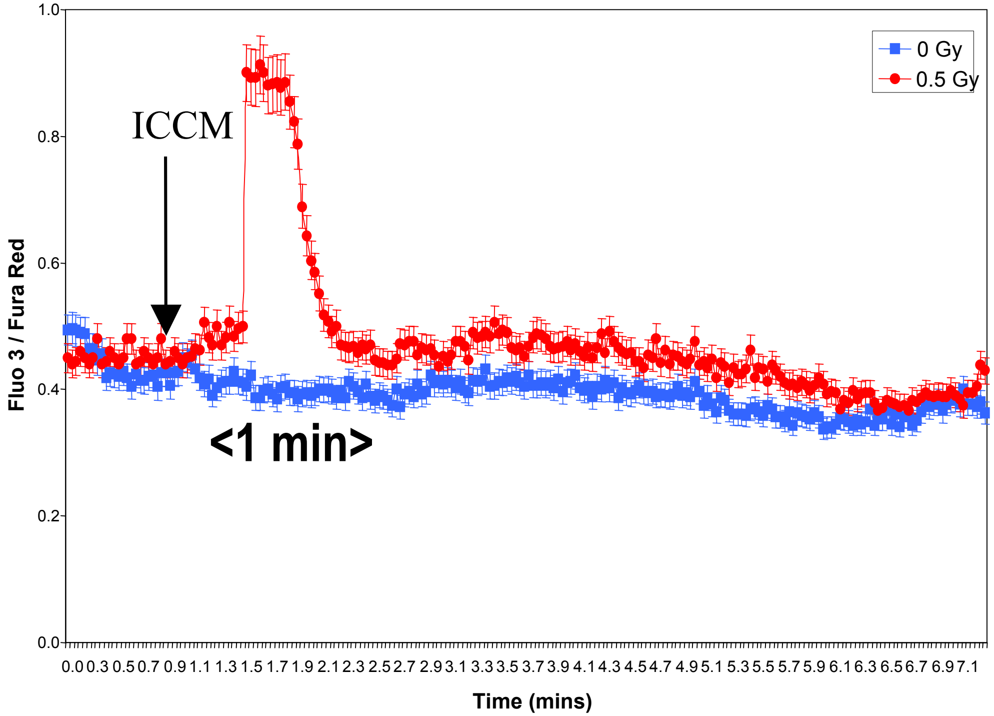
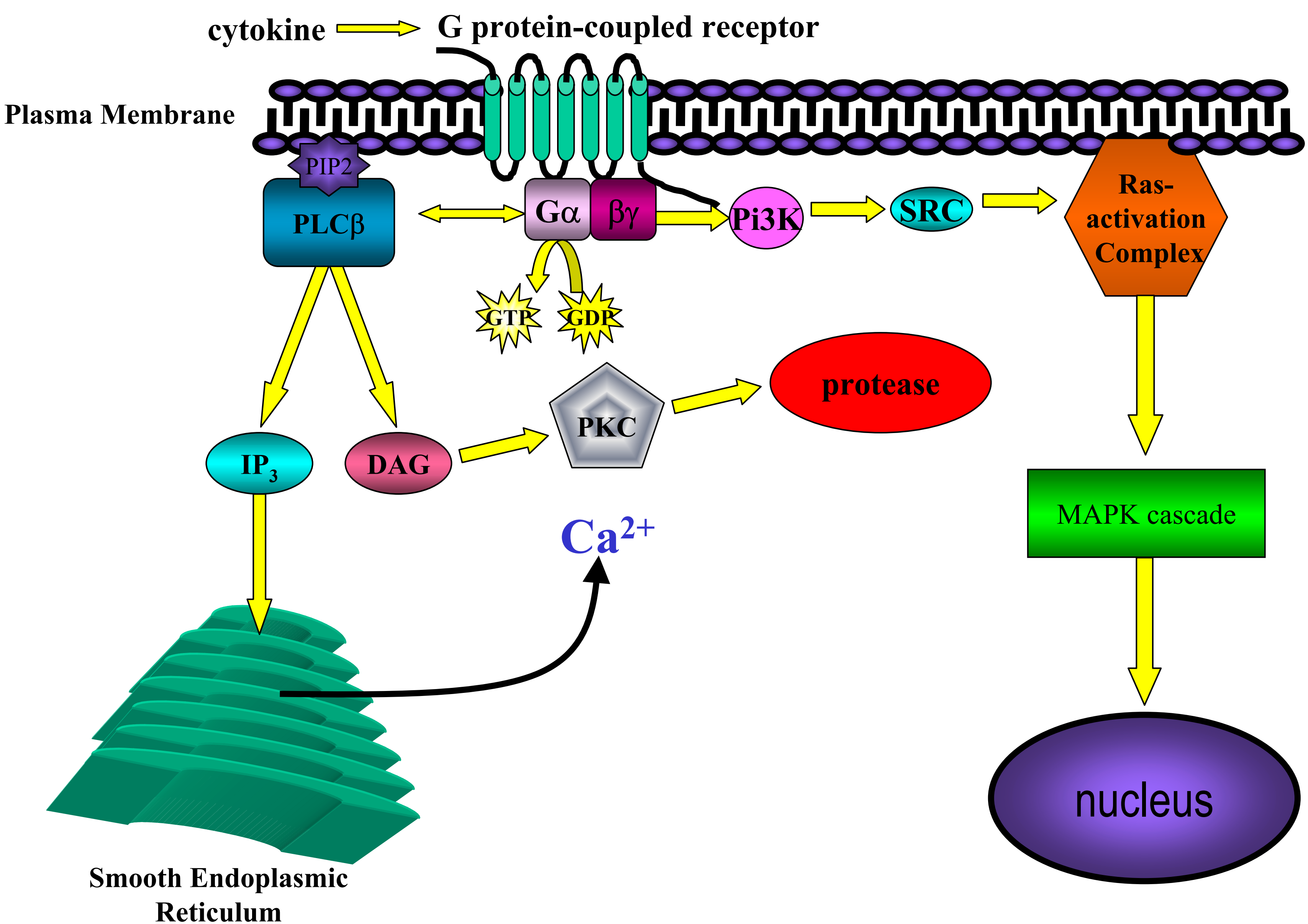


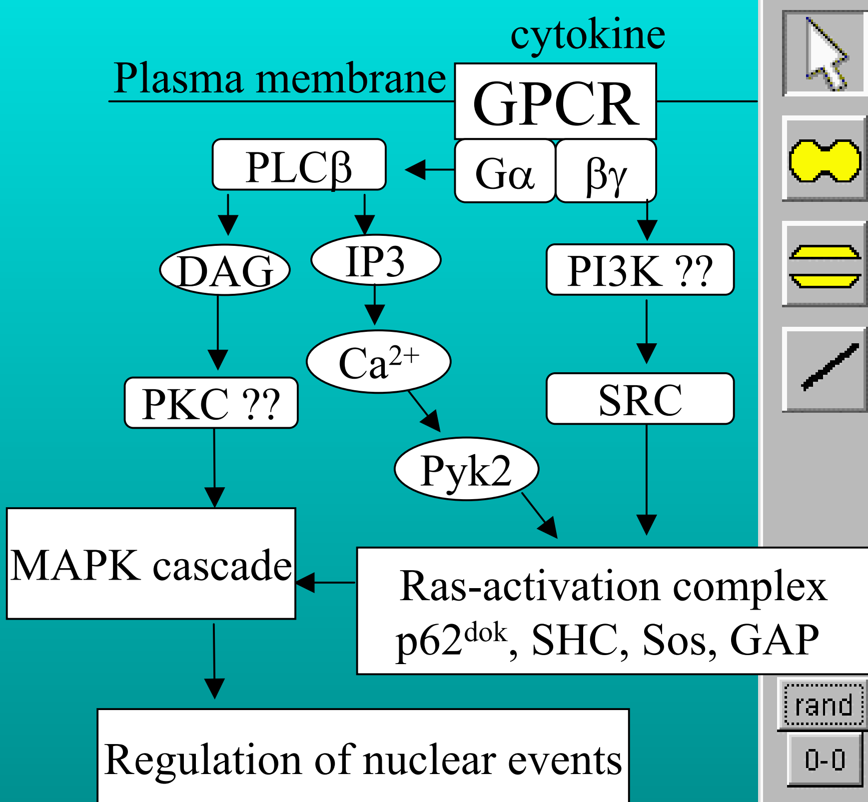
Figure 11. Intracellular calcium levels in HPV -G cells after addition of medium from unirradiated cells (0 Gy ICCM) and medium from irradiated cells (0.5 Gy ICCM). ICCM was added at the time indicated by the arrow. The ratio of the fluorescence emissions from the calcium sensitive dyes Fluo3 and Fura Red provides an indication of intracellular calcium levels.

Model for the Role of Ca^{2+} in Stress-Response Pathways

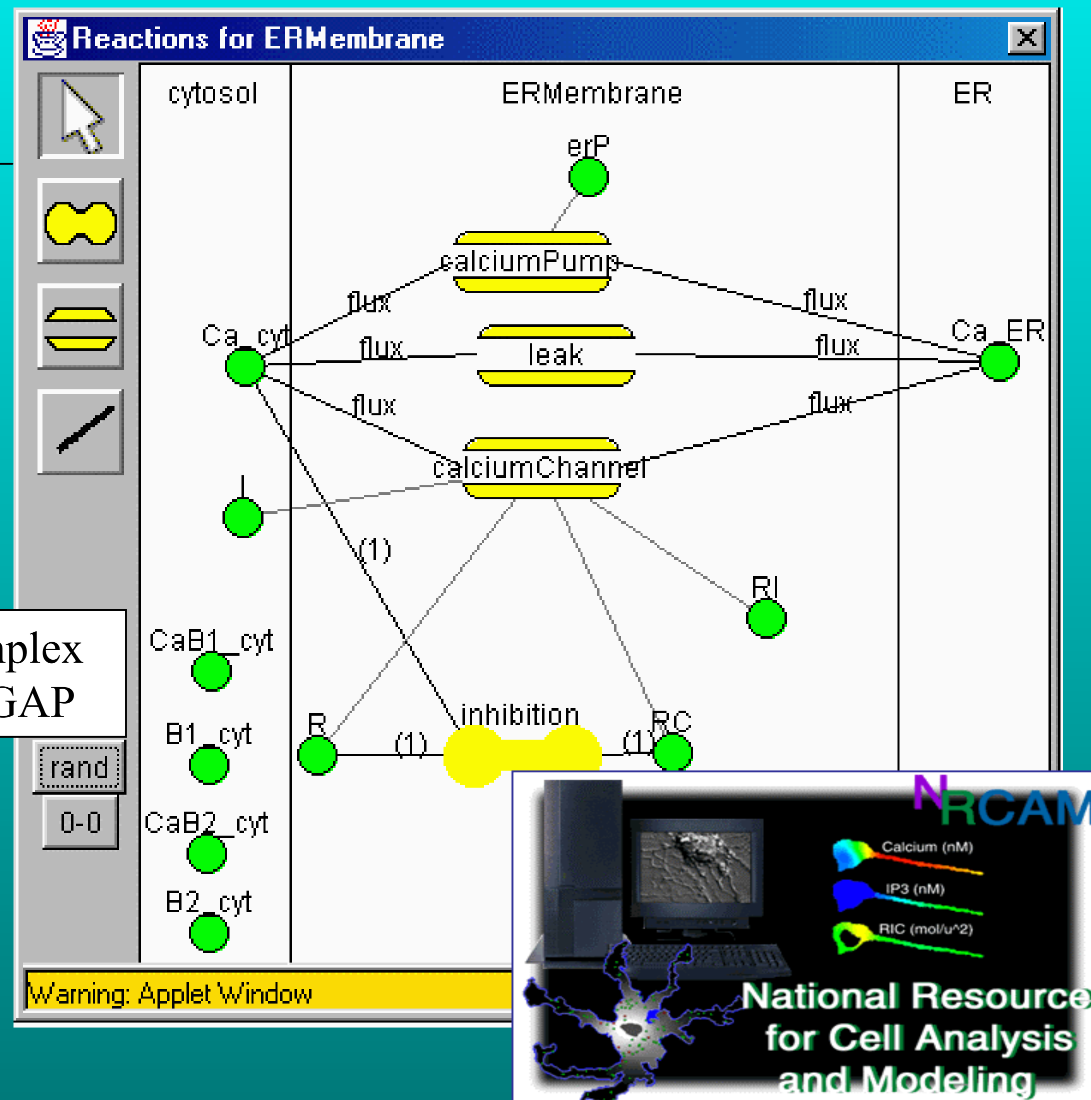


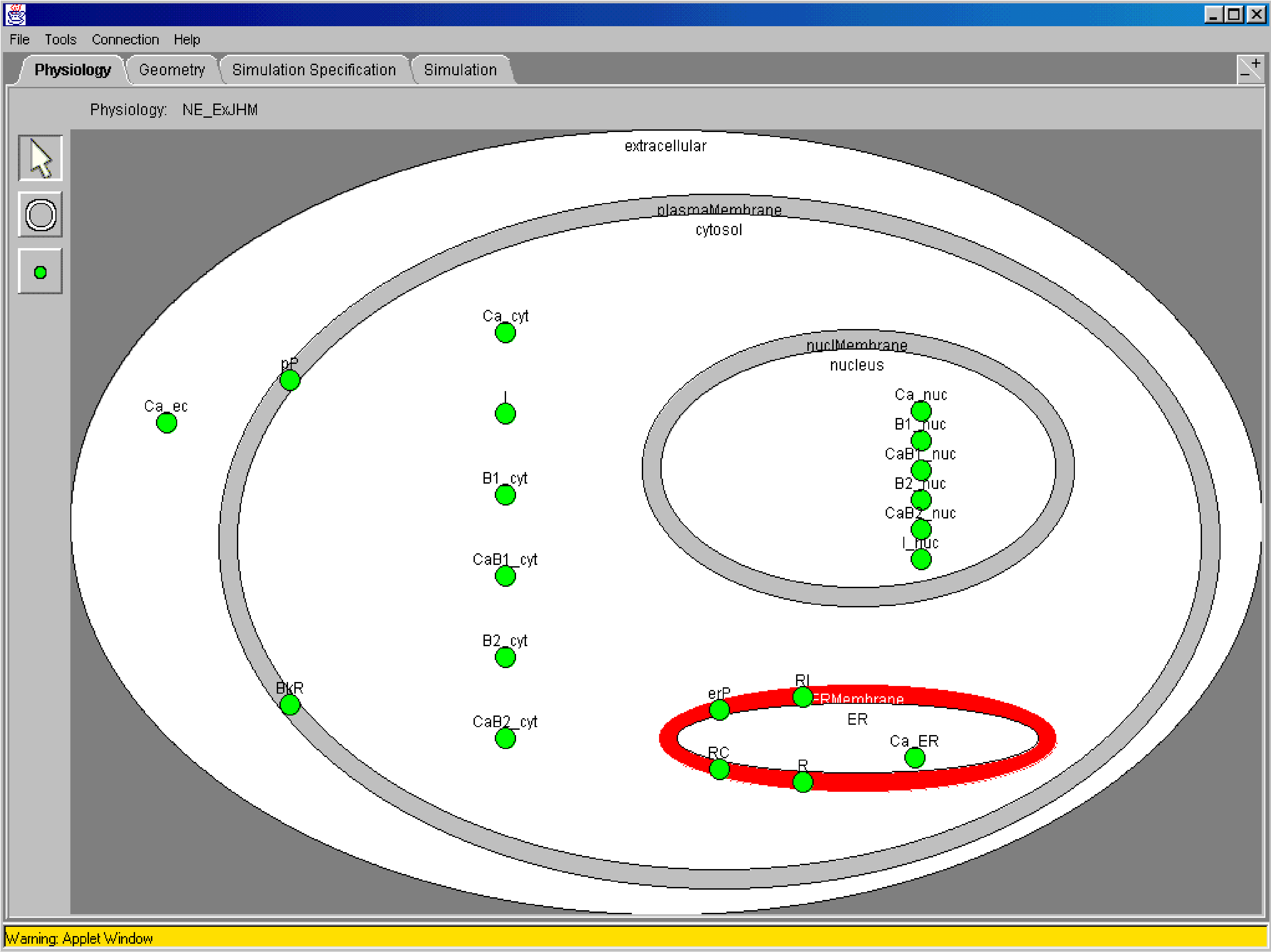
Modeling the production of a Ca pulse using the Virtual Cell

Cell Signaling Pathway



The Virtual Cell

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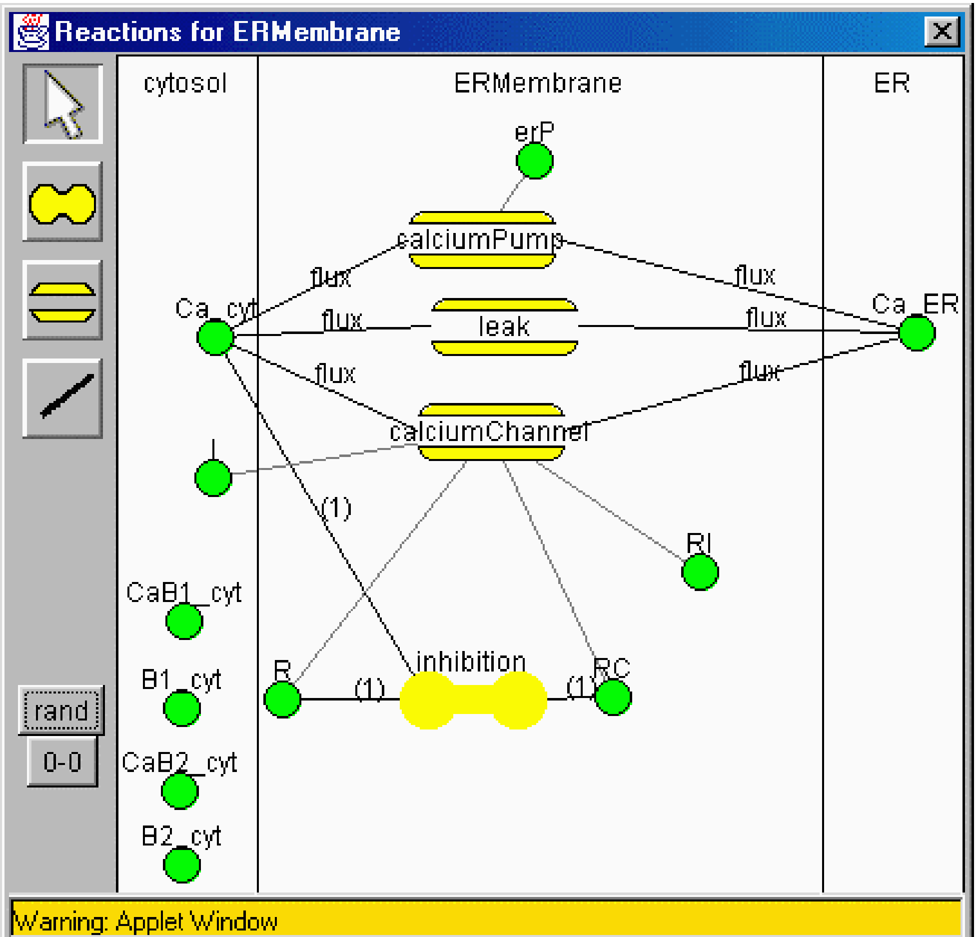
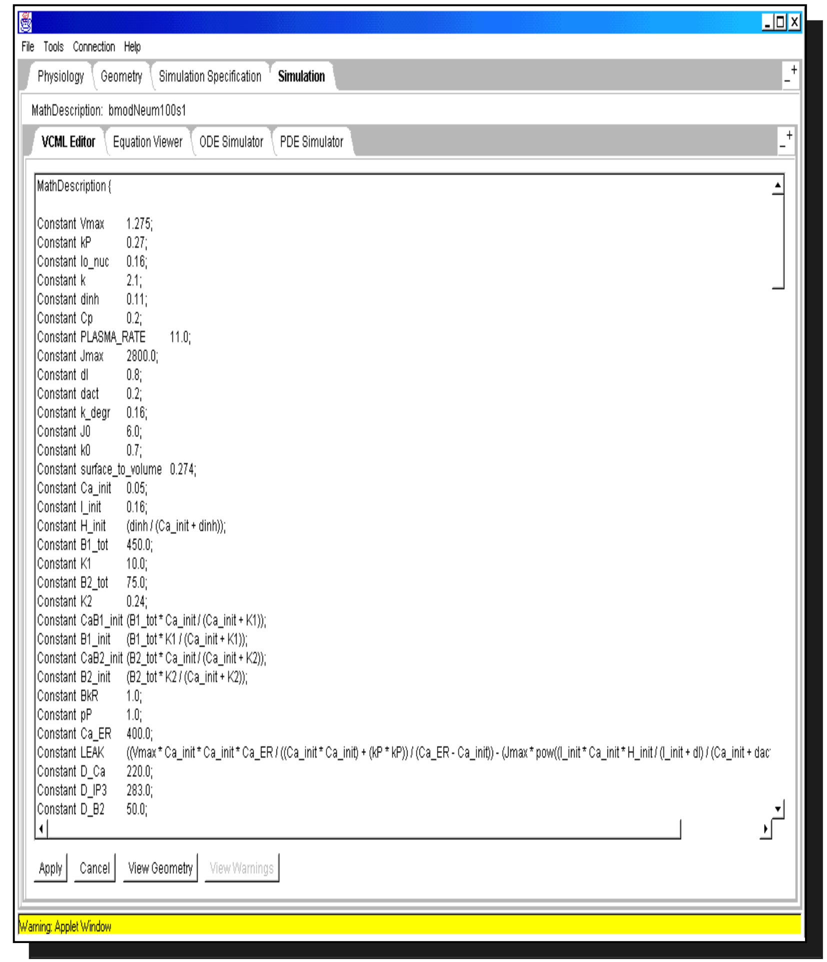
Tools
Connection
Help
Physiology
Geometry
Simulation Specification
Simulation
Physiology: NE_ExJHM
extracellular
plasmaMembrane
cytosol
Ca_cyt
pP
Ca_ec
I
B1_cyt
CaB1_cyt
B2_cyt
CaB2_cyt
BkR
nuclMembrane
nucleus
Ca_nuc
B1_nuc
CaB1_nuc
B2_nuc
CaB2_nuc
I_nuc
erP
RI
ERMembrane
ER
Ca_ER
RC
R
Warning: Applet Window

Symbolic definition of model



Mathematical interpretation



Morphology of Hela Cells Using Confocal Microscopy and Fluorescing Probes

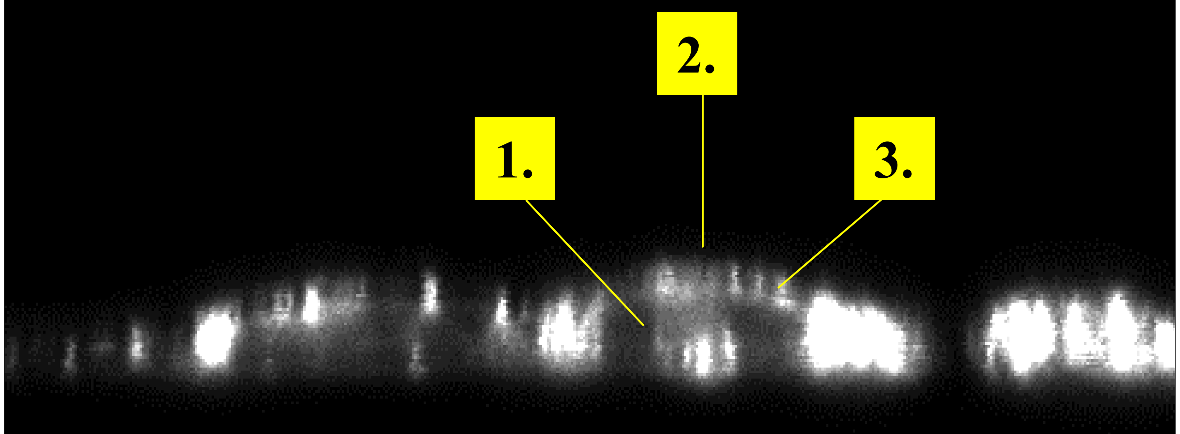
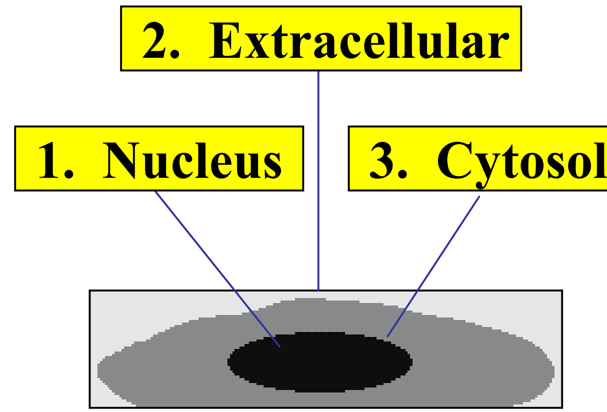
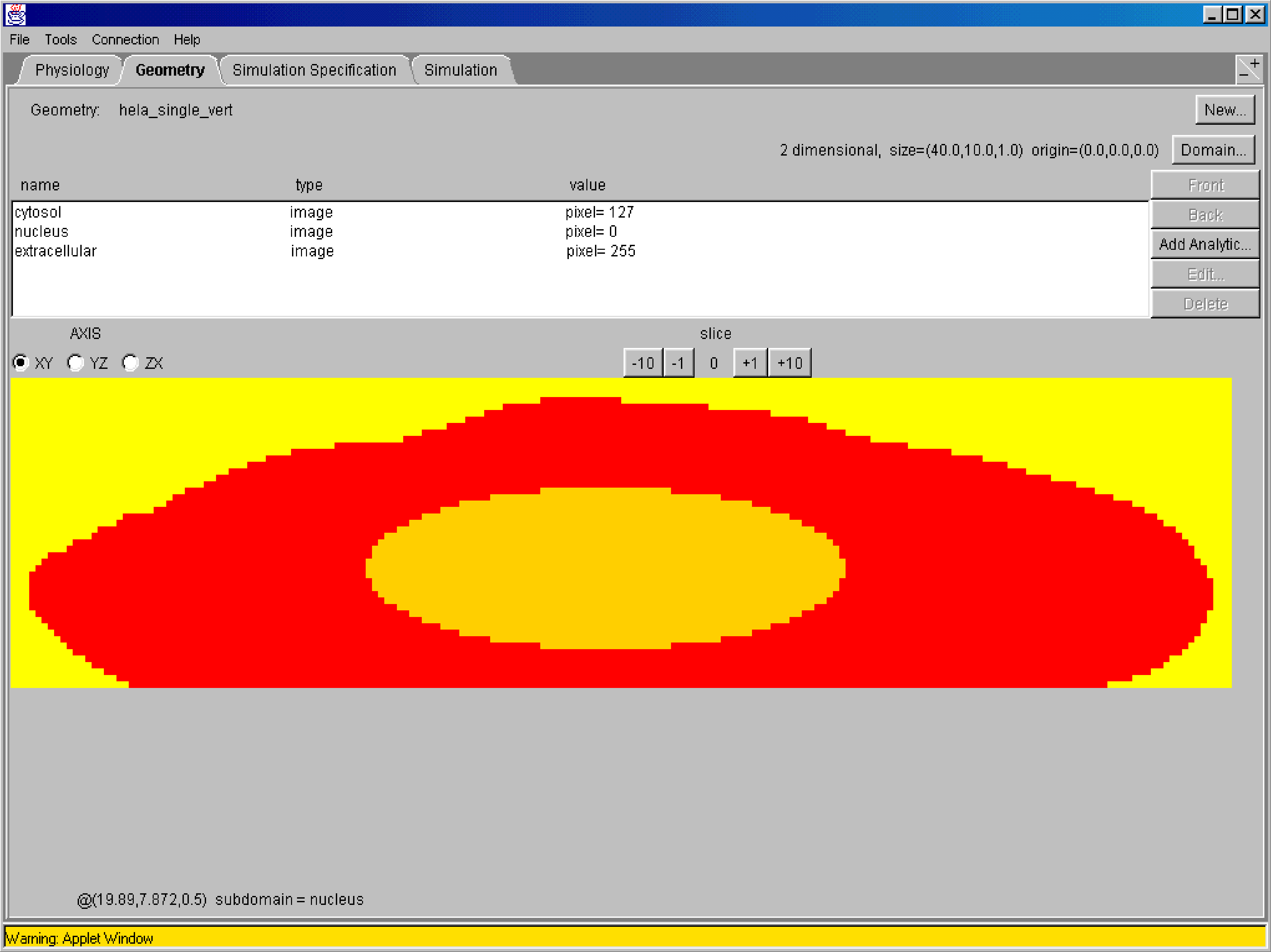


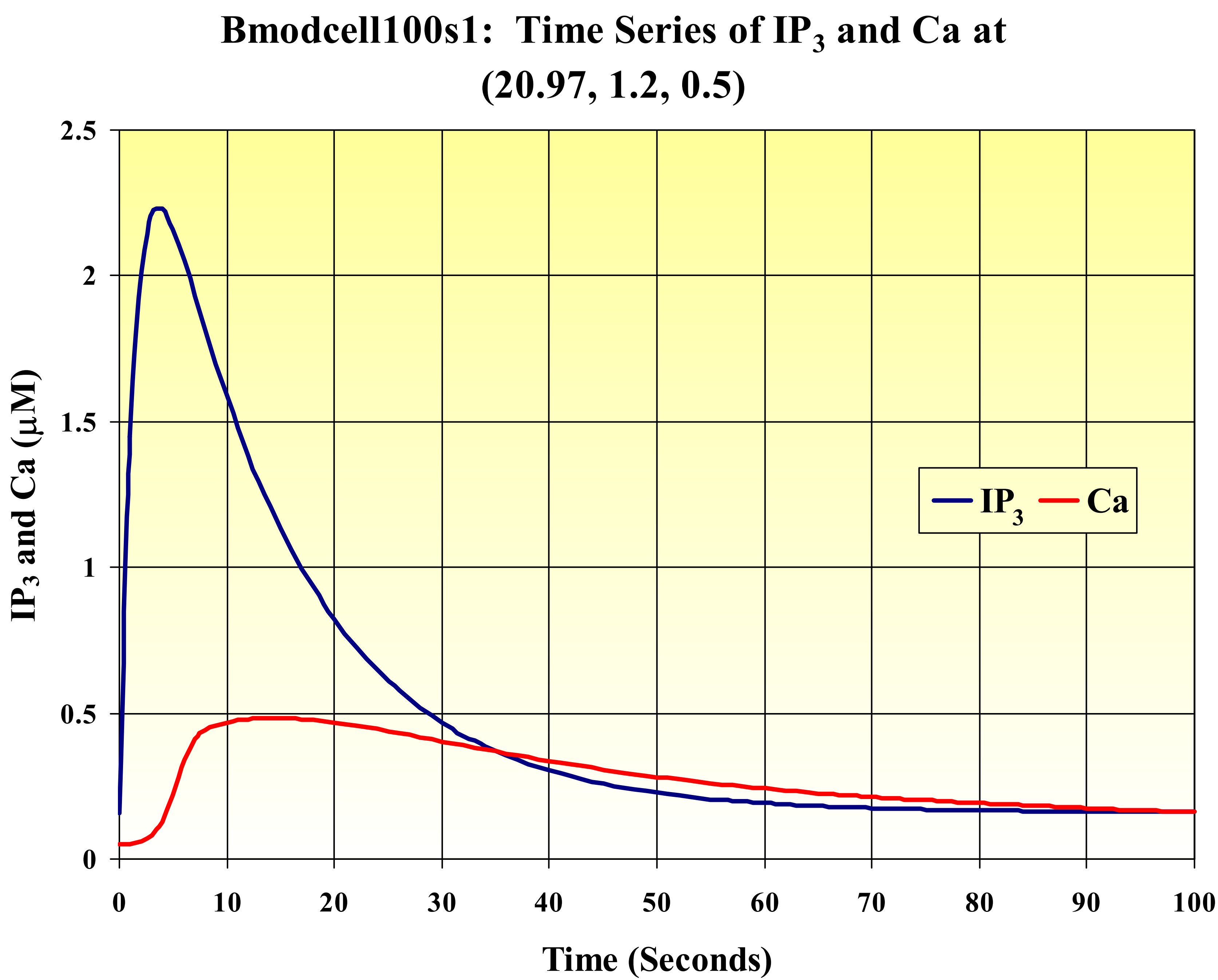
Image of Hela Cell Modified by Photoshop 5.5



Modifications:

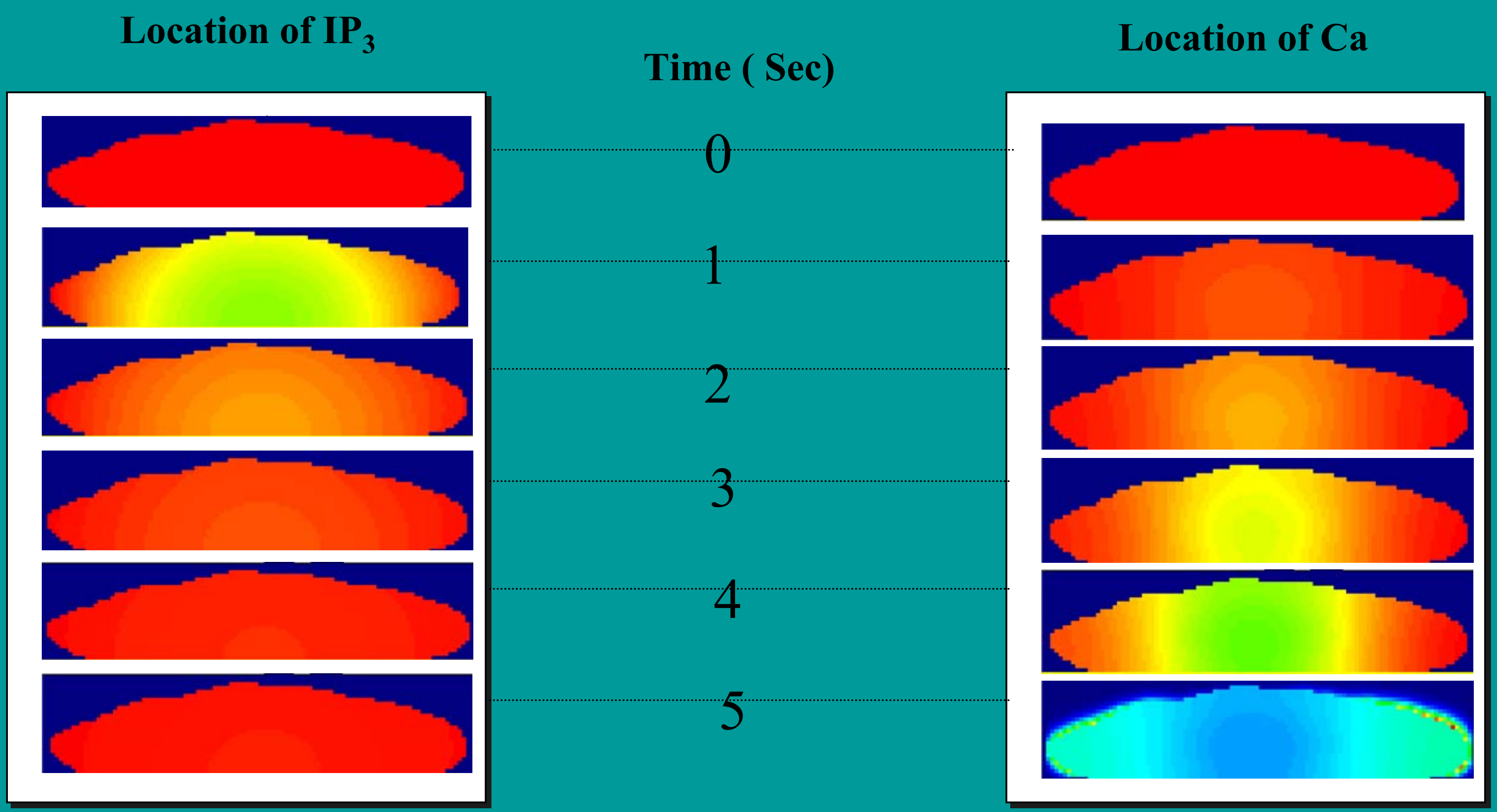
- Cells must have the same number of gray levels as named regions.
- Histogram and Posterizing tools are used to detect gray levels
- CMYK color setting


File Tools Connection Help
Physiology
Geometry
Simulation Specification
Simulation
Geometry: hela_single_vert
New...
2 dimensional, size=(40.0,10.0,1.0) origin=(0.0,0.0,0.0)
Domain...
name
type
value
cytosol image pixel= 127
nucleus image pixel= 0
extracellular image pixel= 255
Front
Back
Add Analytic...
Edit...
Delete
AXIS
XY
YZ
ZX
slice
-10
-1
0
+1
+10
@(19.89,7.872,0.5) subdomain = nucleus
Warning: Applet Window

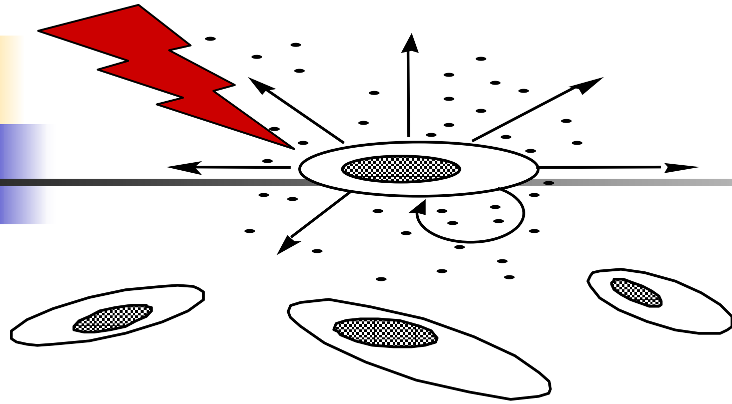


Bmodcell100s1: Time Series of IP_3 and Ca at
(20.97, 1.2, 0.5)
IP_3 and Ca (μM)
2.5
2
1.5
1
0.5
0
0
10
20
30
40
50
60
70
80
90
100
Time (Seconds)
IP_3
Ca

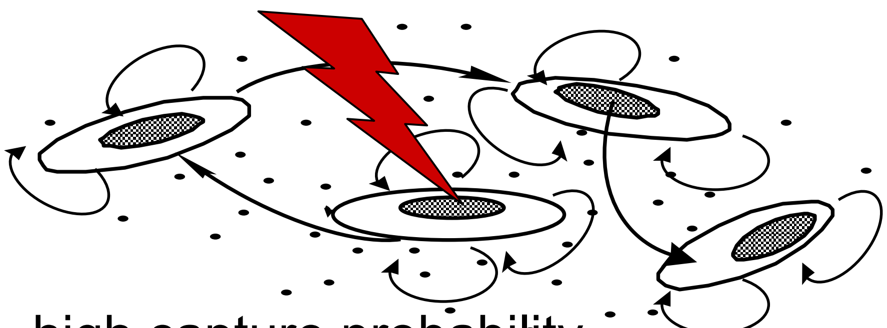
Spatial &Temporal Series



Bystander Signaling by an Autocrine Process

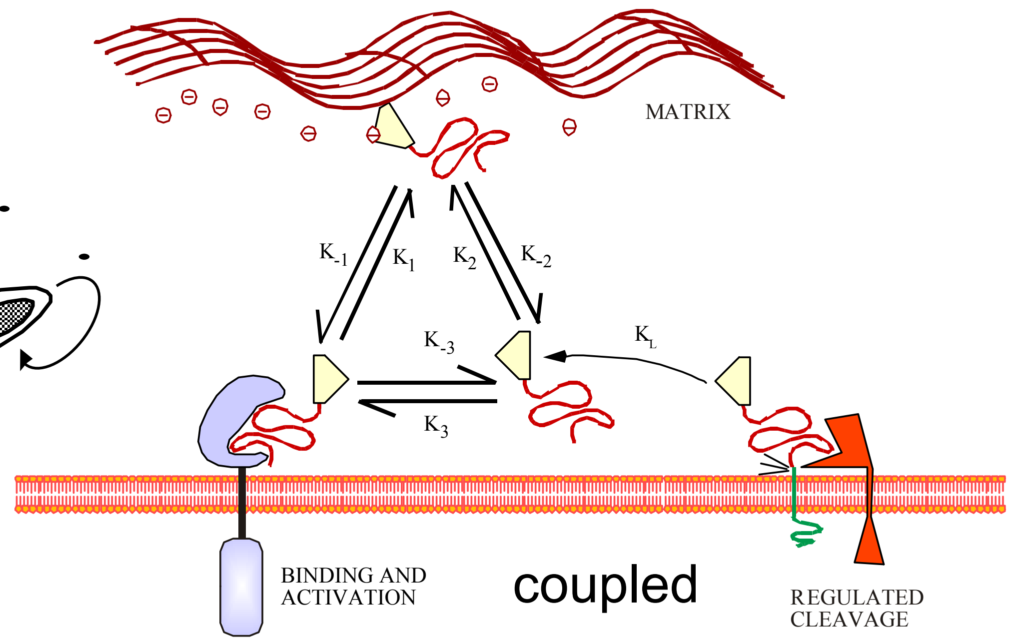


low capture probability
range limited by diffusion

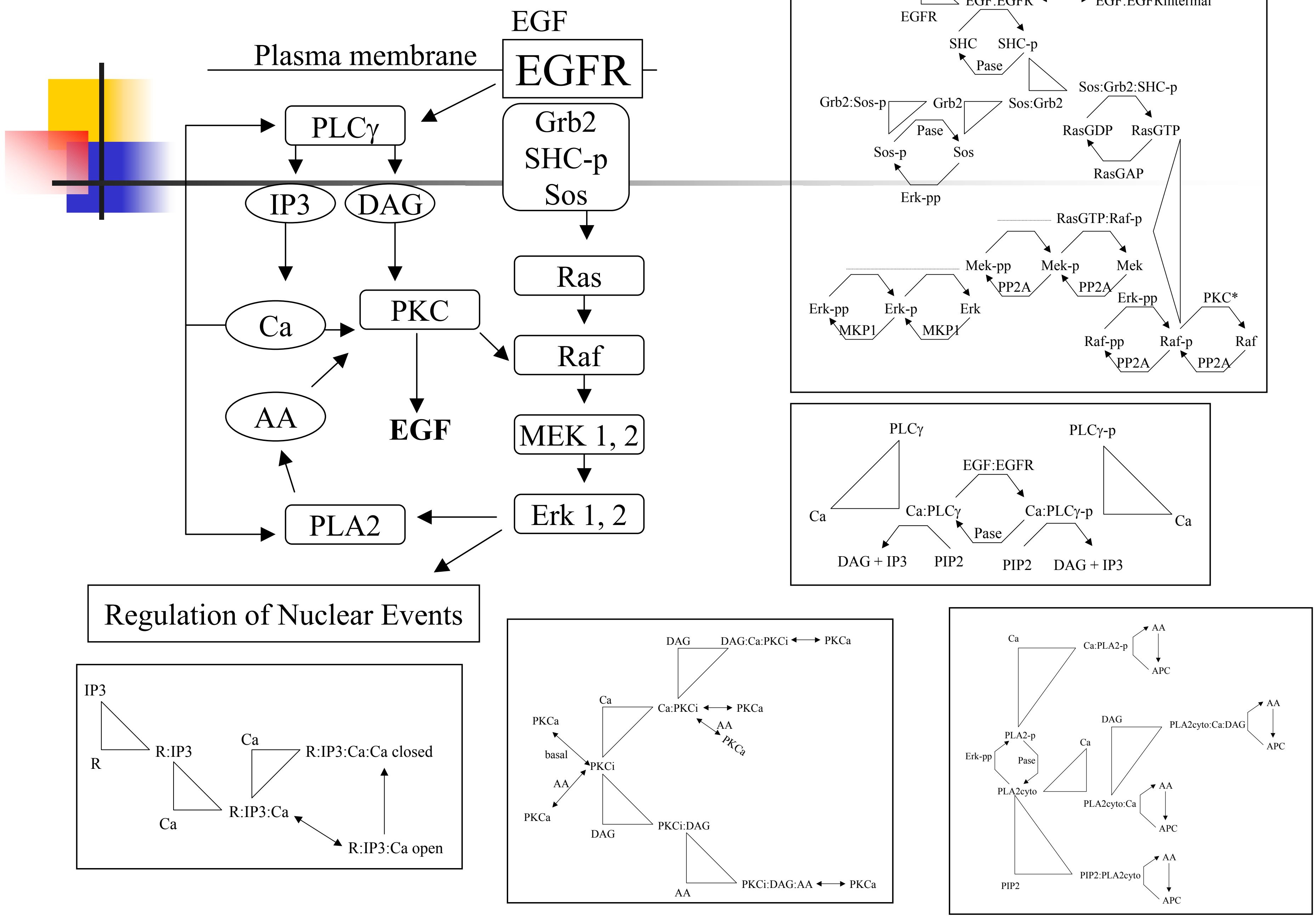


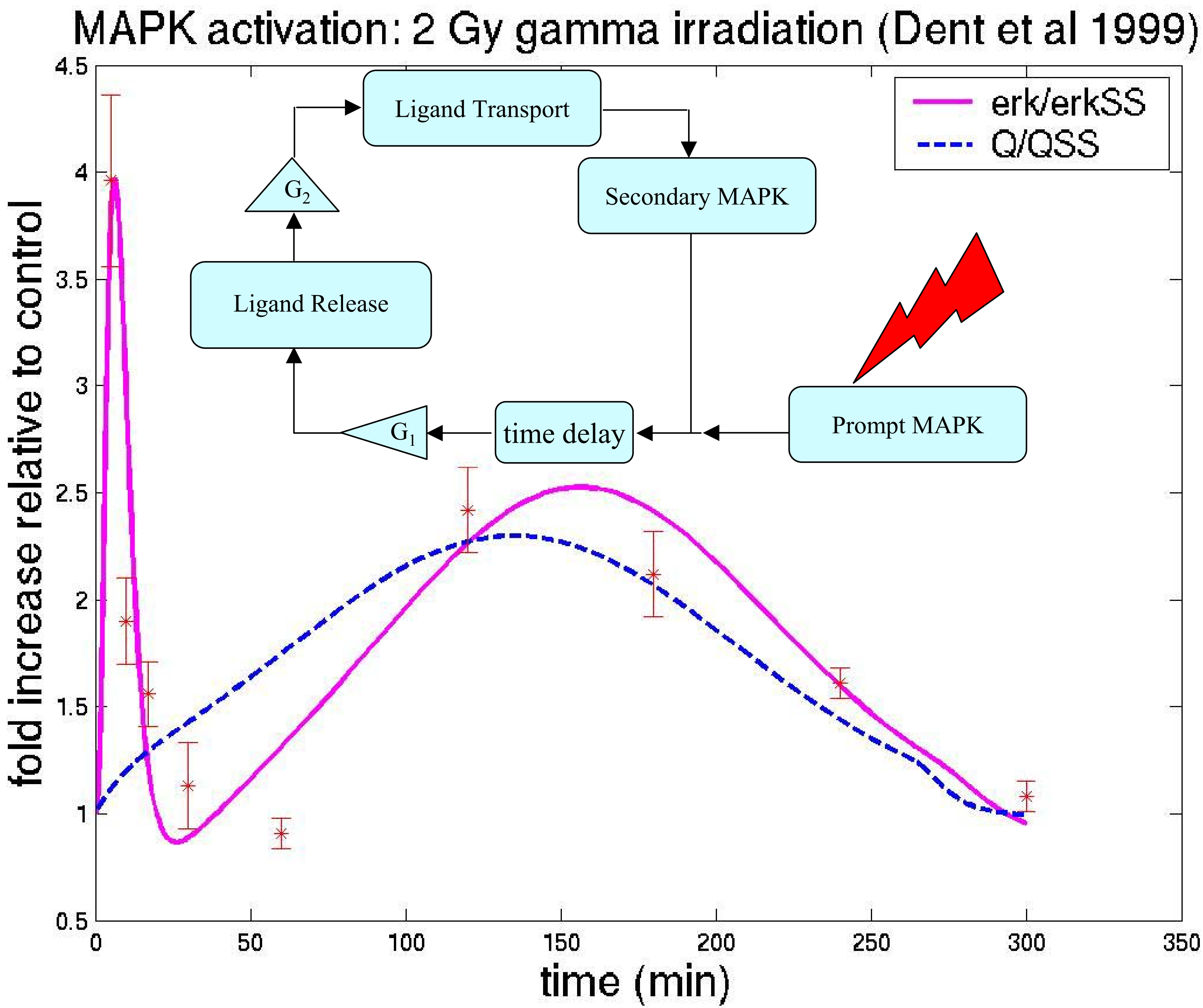
high capture probability
range limited by relay ability

May explain long-range
bystander effects.



Linking Modules into Networks




MAPK activation: 2 Gy gamma irradiation (Dent et al 1999)
erk/erkSS
Q/QSS
Ligand Transport
Secondary MAPK
G2
Ligand Release
G1
time delay
Prompt MAPK
fold increase relative to control
time (min)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
50
100
150
200
250
300
350

Radiation-Induced Release of Epidermal Growth Factor