NATIONAL BIOMEDICAL COMPUTATION RESOURCE

Conduct, catalyze and enable multiscale biomedical research

Effects of 3D t-tubule anatomy on Ca2+ signaling in rodent ventricular myocytes with inhibited sarcoplasmic reticulum

Yuhui Cheng and Anushka Michailova

NBCR Summer Institute

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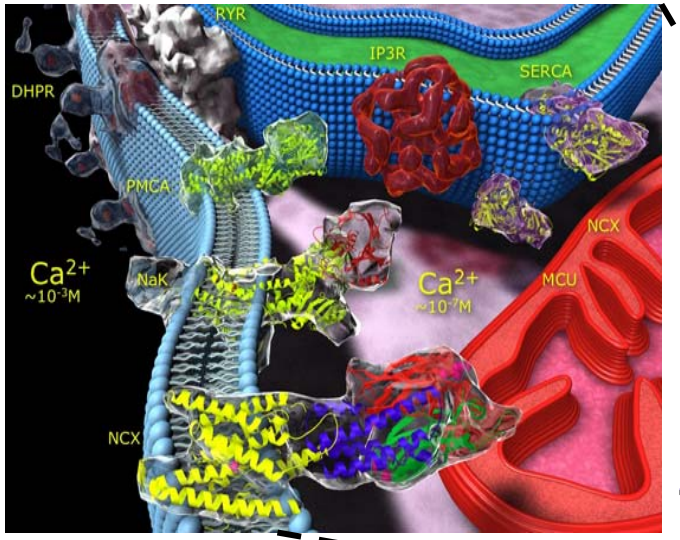
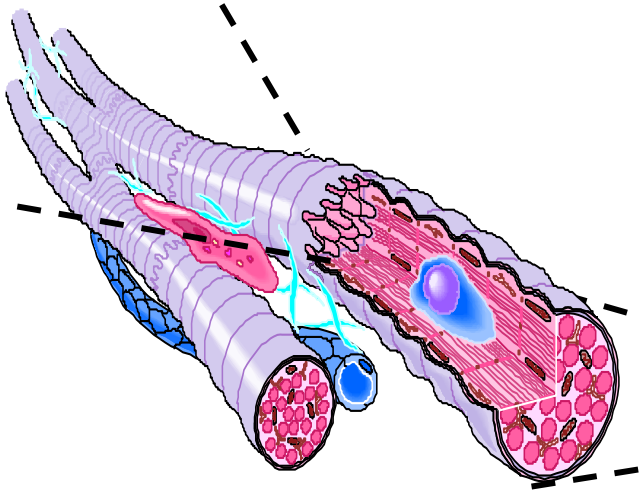
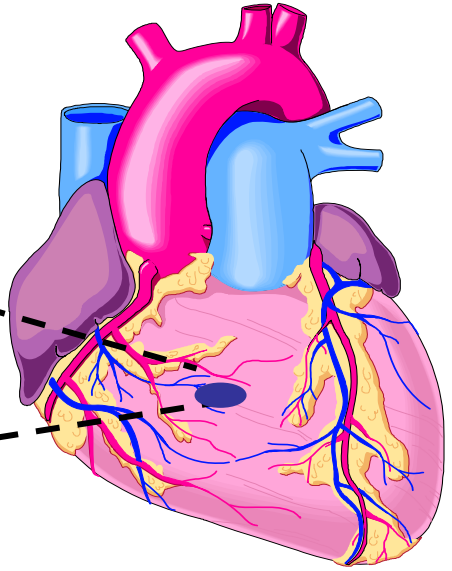
http://mccammon.ucsd.edu/smol/doc/tutorials/nbcr080709_lab.pdf

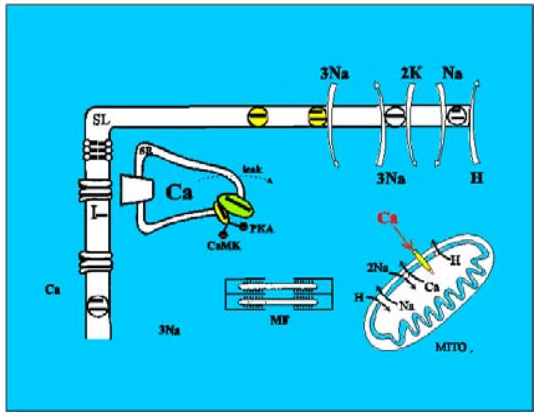
To understand how the normal heart functions and becomes dysfunctional in patho-physiological states requires comprehension at multiple levels from ion channel to cell and organ.

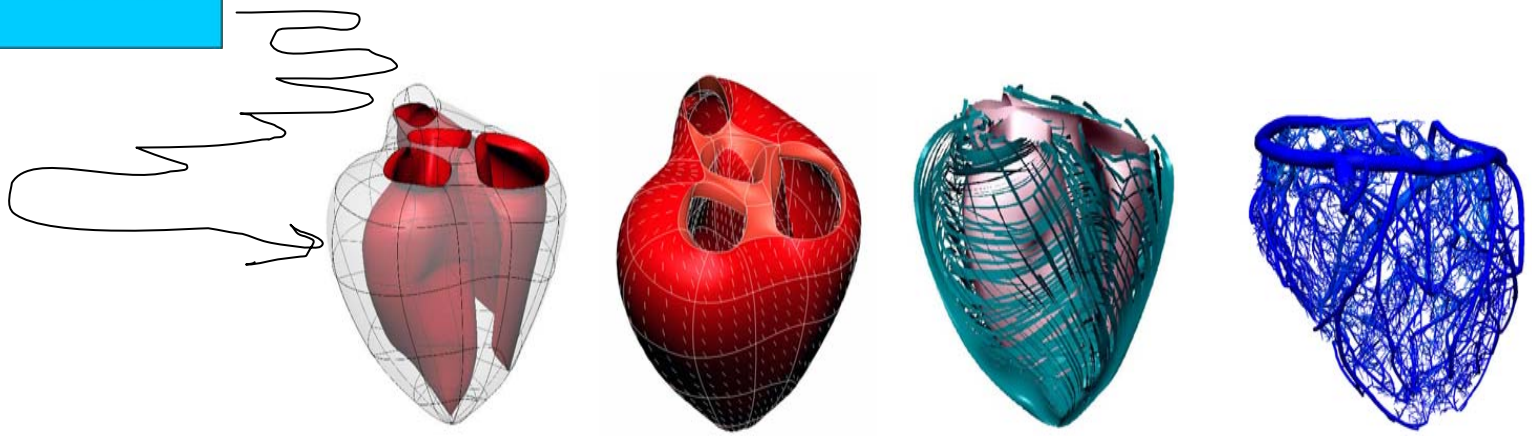






Remarkable amount of fundamental quantitative data on the cardiac cell structure, ionic fluxes, intracellular Ca^{2+} homeostasis have been accumulated. It is now equally important to integrate this wealth of information in the form of predictive, structural and functional computational sub-cellular and cellular models and to link this model to tissue and whole heart physiology models.





Objectives

- Mesh generation.
- The fundamentals of GMV Mesh Viewer.
- Experiment 1: To show the Ca^{2+} concentration distribution in the compartment.
- Experiment 2: To draw scan lines.
- References.

Mathematical background

$$\frac{\partial [Ca^{2+}]_i}{\partial t} = D_{Ca} \nabla^2 [Ca^{2+}]_i - \sum_{m=1}^{3} R_{B_m} - R_{B_s} + J_{Ca\,flux}$$

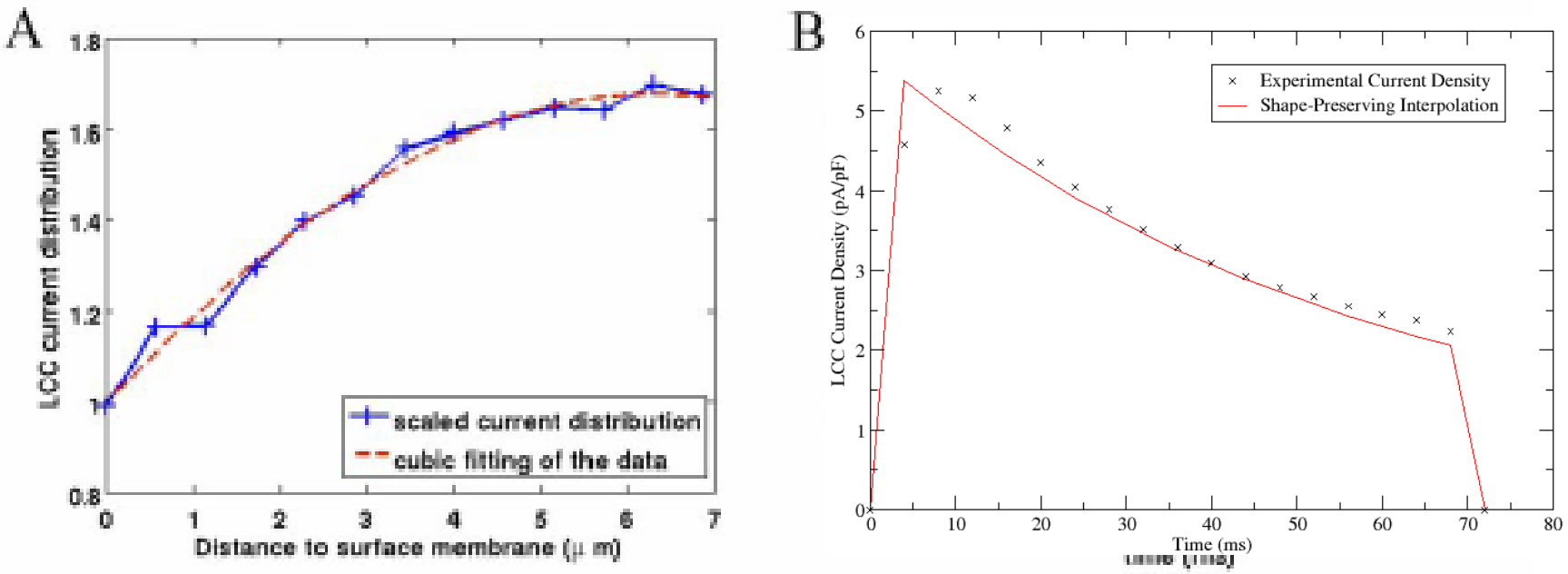
$$\frac{\partial [CaB_m]}{\partial t} = D_{CaB_m} \nabla^2 [CaB_m] + R_{B_m}$$

$$\frac{\partial [CaB_s]}{\partial t} = R_{B_s}$$

$$R_{B_m} = k_+^m ([B_m] - [CaB_m])[Ca^{2+}]_i - k_-^m [CaB_m]$$

$$R_{B_s} = k_+^s ([B_s] - [CaB_s])[Ca^{2+}]_i - k_-^s [CaB_s]$$

L-type Ca^{2+} ion channel density



$$I_{LCC}(t) = I_{LCC0} f(t)$$

Figure 2.

$$f(t) = \begin{cases} 0.05978t & 0 < t < t_{a1} \\ 0.02327 + 0.11931e^{-\frac{t}{55.90035}} + 0.11931e^{-\frac{t}{55.89166}} & t_{a1} \le t < t_{a2} \\ 0 & t \ge t_{a2} \end{cases}$$

Na^+/Ca^{2+} exchanger and Ca^{2+} leak

$$I_{NCX} = g_{NCX} \frac{e^{\eta VF/RT}[Na^+]_i^3[Ca^{2+}]_e - e^{(\eta-1)VF/RT}[Na^+]_e^3[Ca^{2+}]_i}{(k_{m,Na}^3 + [Na^+]_e^3)(k_{m,Ca} + [Ca^{2+}]_e)(1 + k_{sat}e^{(\eta-1)VF/RT})}$$

$$I_{M\_leak} = g_{M\_leak}\left([Ca^{2+}]_e - [Ca^{2+}]_i\right)$$

When the cell is at the resting state, $I_{NCX}=I_{M\_leak}$

$$J_i = \left(\frac{1}{2F}\frac{C_i}{V_i}\right)I_i$$

$$J_{Ca_{flux}} = J_{Ca} - J_{NCX} + J_{M\_leak}$$

Software Design

GAMer : Mesher generator.

"main.c" : Define the shell and several input parameters.

"myroutines.c" : Subroutines for reading the input parameters; linear solver; output format controller

"mypde.c" : Define the 4 PDEs that we try to solve.

"tsolve.c" : Define surface flux; time-dependent linear solver

"mysolv.c" : Standard linear solvers. (needn't modify)

Sample Input File

```
DRG
  conc_cae 1000.0   /* external Ca2+ concentration. */
  conc_cai 0.1      /* internal Ca2+ concentration. */
  diff_ca  0.39     /* Ca2+ diffusion coefficient */
  T        300.0    /* cell temperature. */
  kcat     30.0     /* flux scale parameter. */
end
TN
  conc_tn   70
  diff_tn   1.0
  kptn      0.04
  kmtn      0.04
end
...
...
end
Cab
  gcab      1.65e-2
end
mesh ../mesh/ttubule2.m /* input mesh file */
end
```

/* buffer and surface flux parameters. */

Manage your input parameters

- NOTE:

${solver}

- the default input file: smol.in

${solver} -ifnam filename

- the default iteration method: CG(lkey=2).

BCG (lkey=4 or 5), BCGSTAB(lkey=6)

${solver} -lkey 2

- default maximal number of iterative steps: 5000

${solver} –lmax 8000

Manage your input parameters (cont.)

- NOTE:
- the default timestep: $5.0*10^{-6}\mu s$

${solver} -dt $5.0*10^{-5}$

- the default number of time steps:500

${solver} –nstep 1000

- the default concentration output frequency: 50

${solver} –cfreq 100

- the default reactive integral output frequency: 1

${solver} –efreq 5

- the default restart file writing frequency: 1000

${solver} –pfreq 5000

GMV Mesh Viewer

You can obtain the GMV mesh viewer via the below link:

http://www-xdiv.lanl.gov/XCM/gmv/GMVHome.html

The user manual can be found here:

http://www-xdiv.lanl.gov/XCM/gmv/doc.color.pdf

Ca^{2+} concentration distribution

NOTE:

cp –r /u/ieng6/nbcr09/nbcr09/public/smol2009 $HOME/smol2009

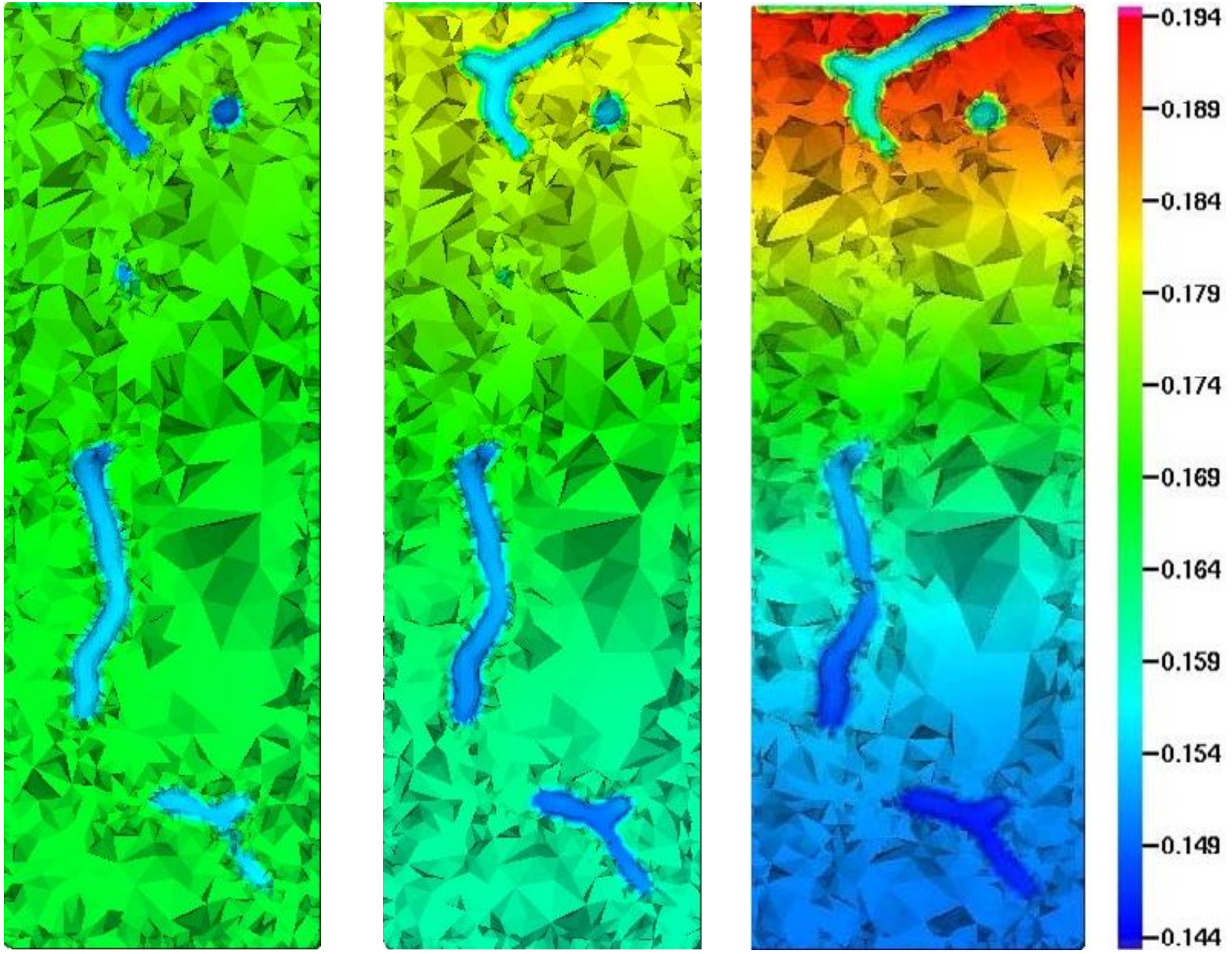
cd $HOME/smol2009

source bashrc

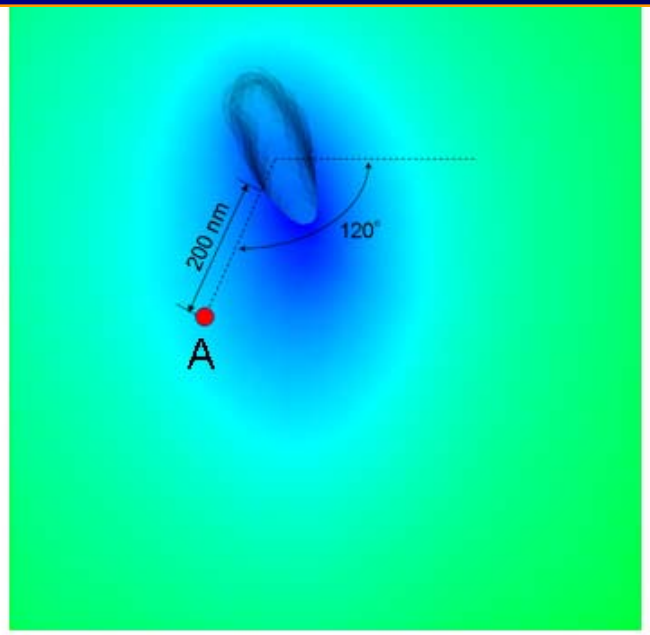
cd $HOME/smol2009/run/calcium/fluo

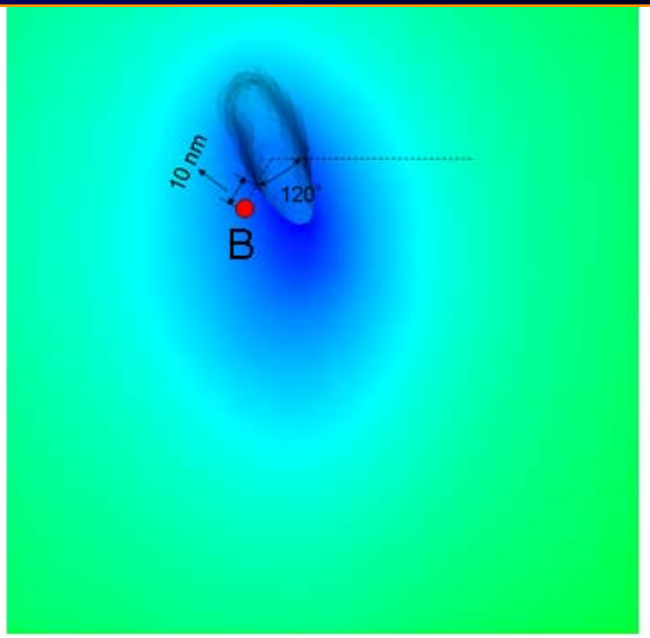
linuxMesa

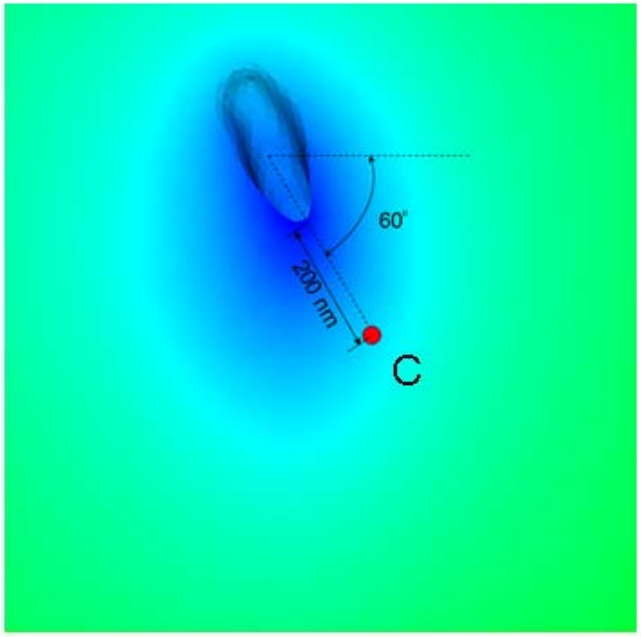
Ca^{2+} concentration distribution

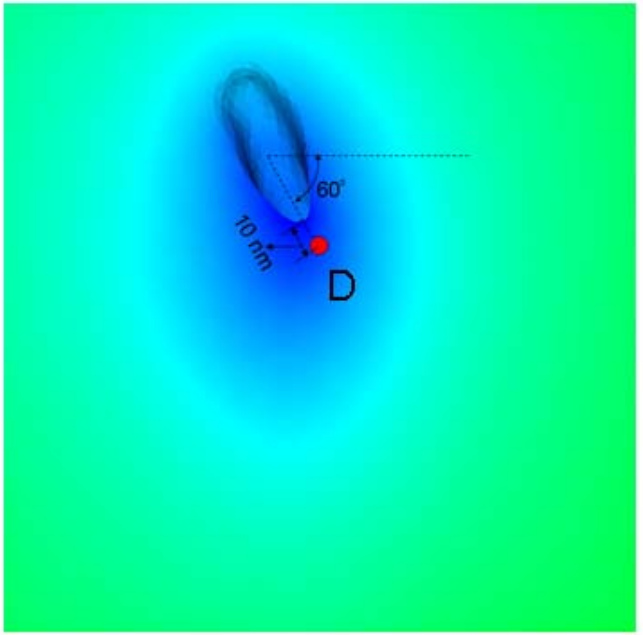


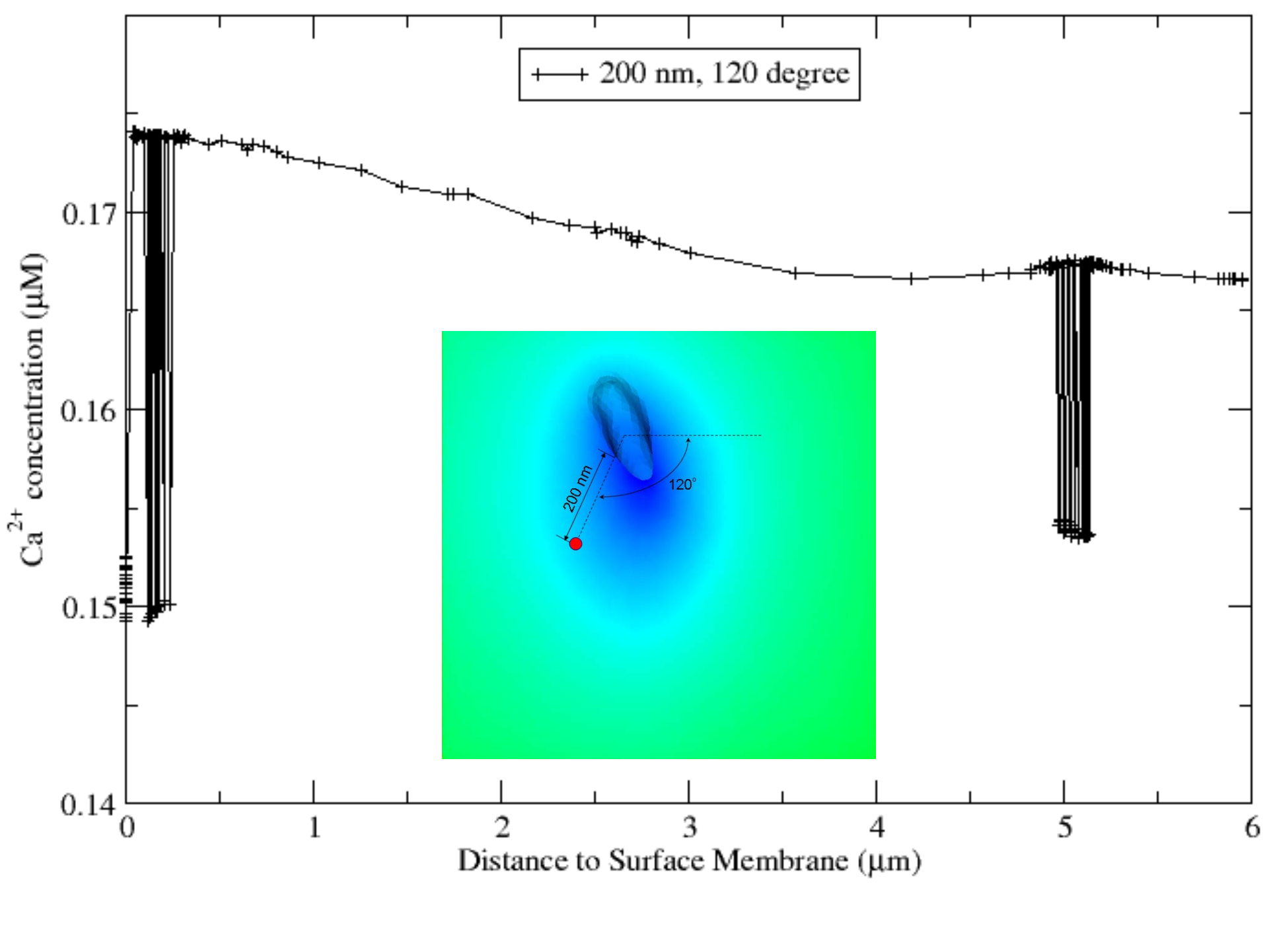
Scan line drawing

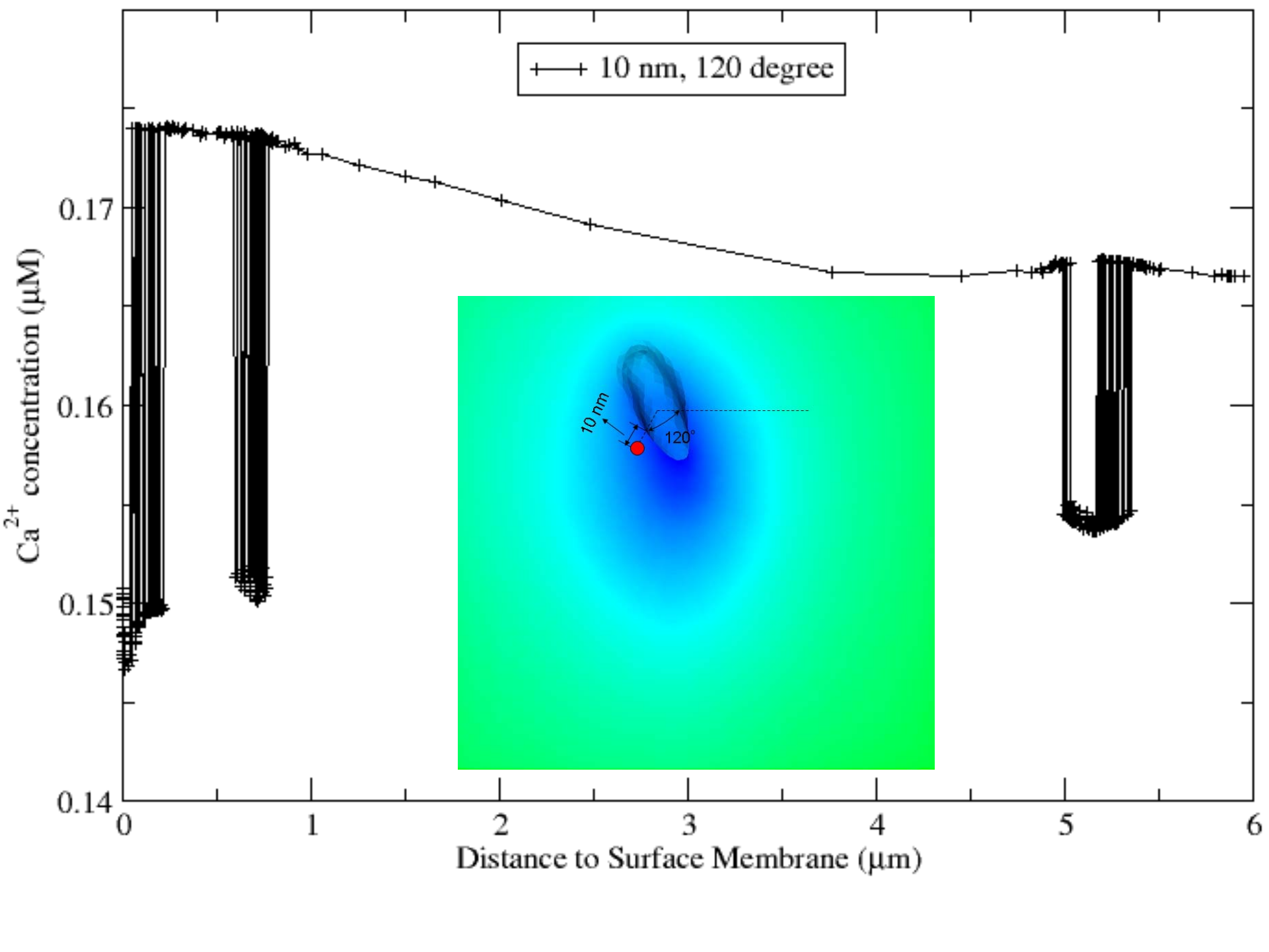


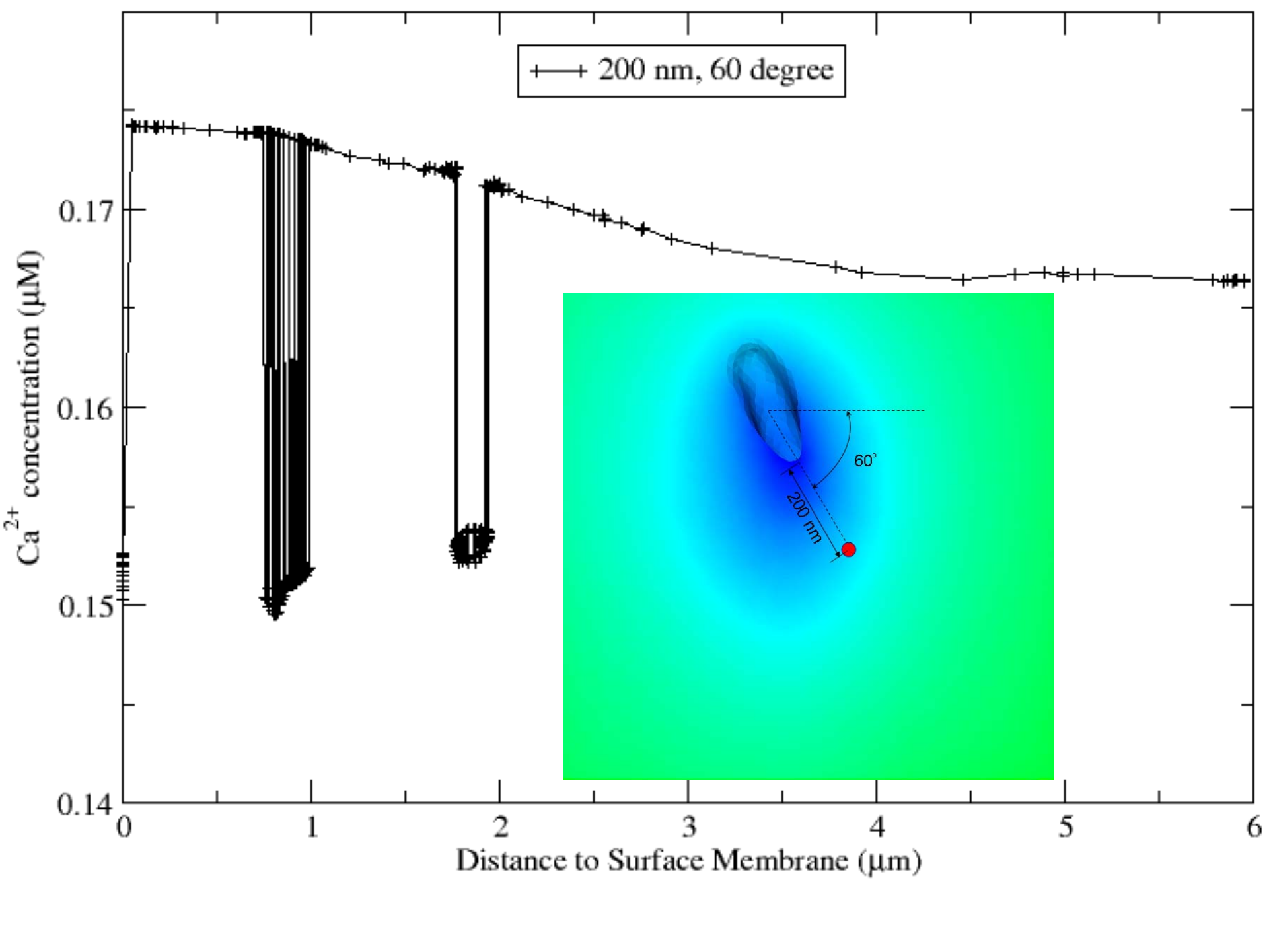


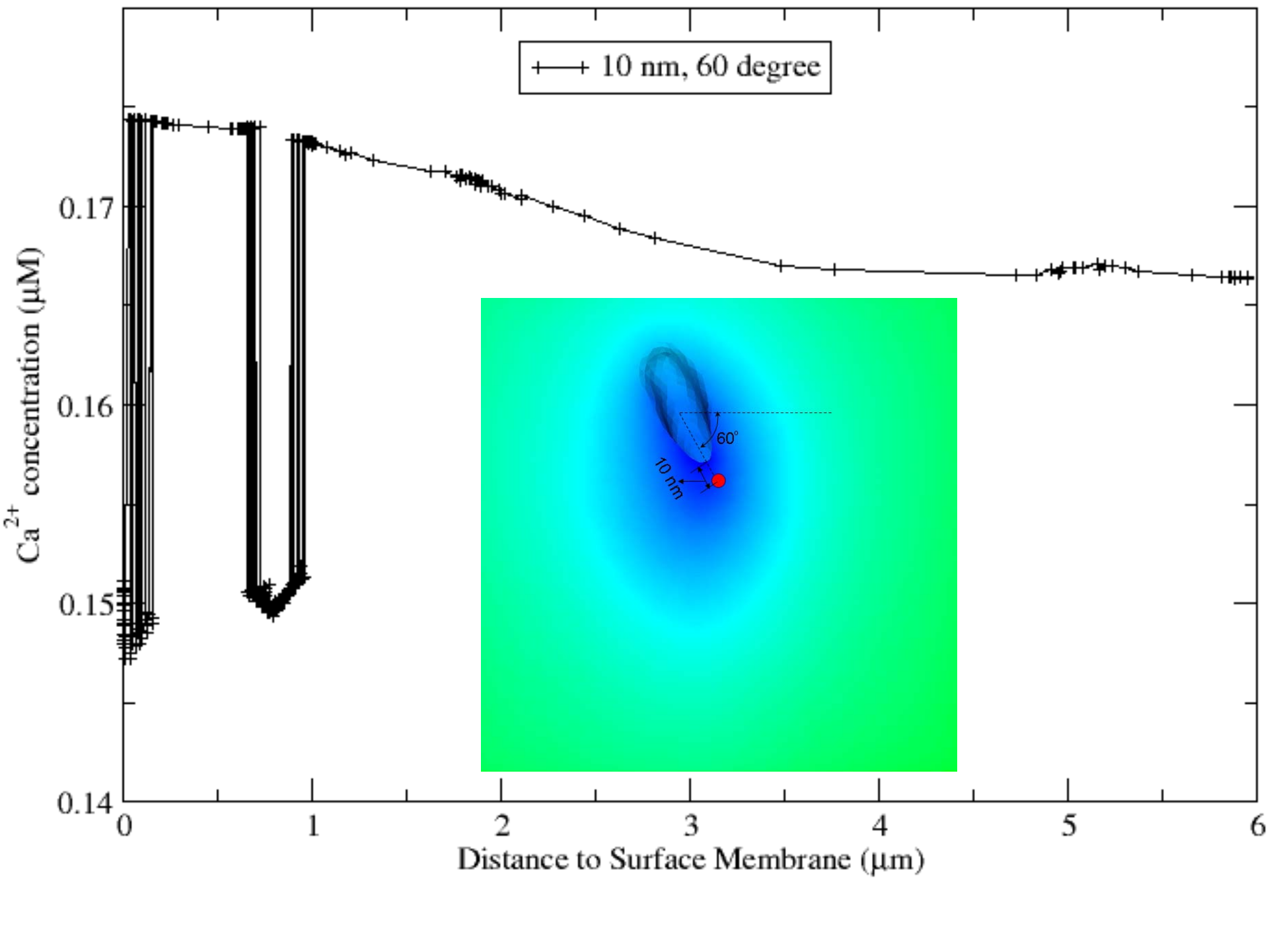





200 nm, 120 degree
0.17
0.16
0.15
0.14
Ca2+ concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)
200 nm
120°


10 nm, 120 degree
0.17
0.16
0.15
0.14
Ca^{2+} concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)
10 nm
120°


200 nm, 60 degree
0.17
0.16
0.15
0.14
Ca^{2+} concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)
60°
200 nm


10 nm, 60 degree
0.17
0.16
0.15
0.14
Ca2+ concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)
60°
10 nm

Scan line drawing

linuxMesa->Calculate->Cutlines->Select Cutlinee (1 NONE)

	X	Y	Z
case 1:	0.0	0.864	1.118
	5.960	0.864	1.118
case 2:	0.0	0.959	1.283
	5.960	0.959	1.283
case 3:	0.0	1.296	1.118
	5.960	1.296	1.118
case 4:	0.0	1.201	1.283
	5.960	1.201	1.283

Ca^{2+} concentration distribution (no fluo-3)

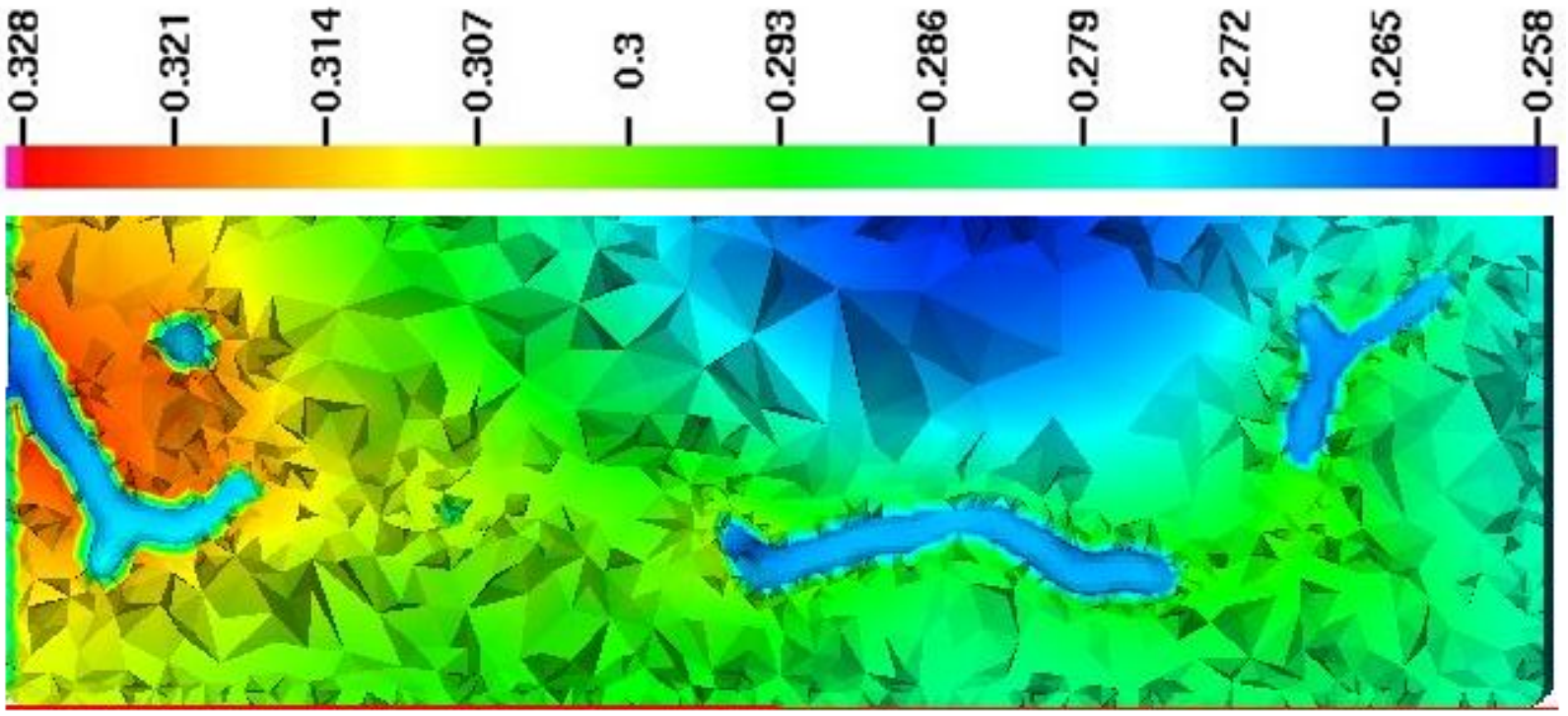
NOTE:

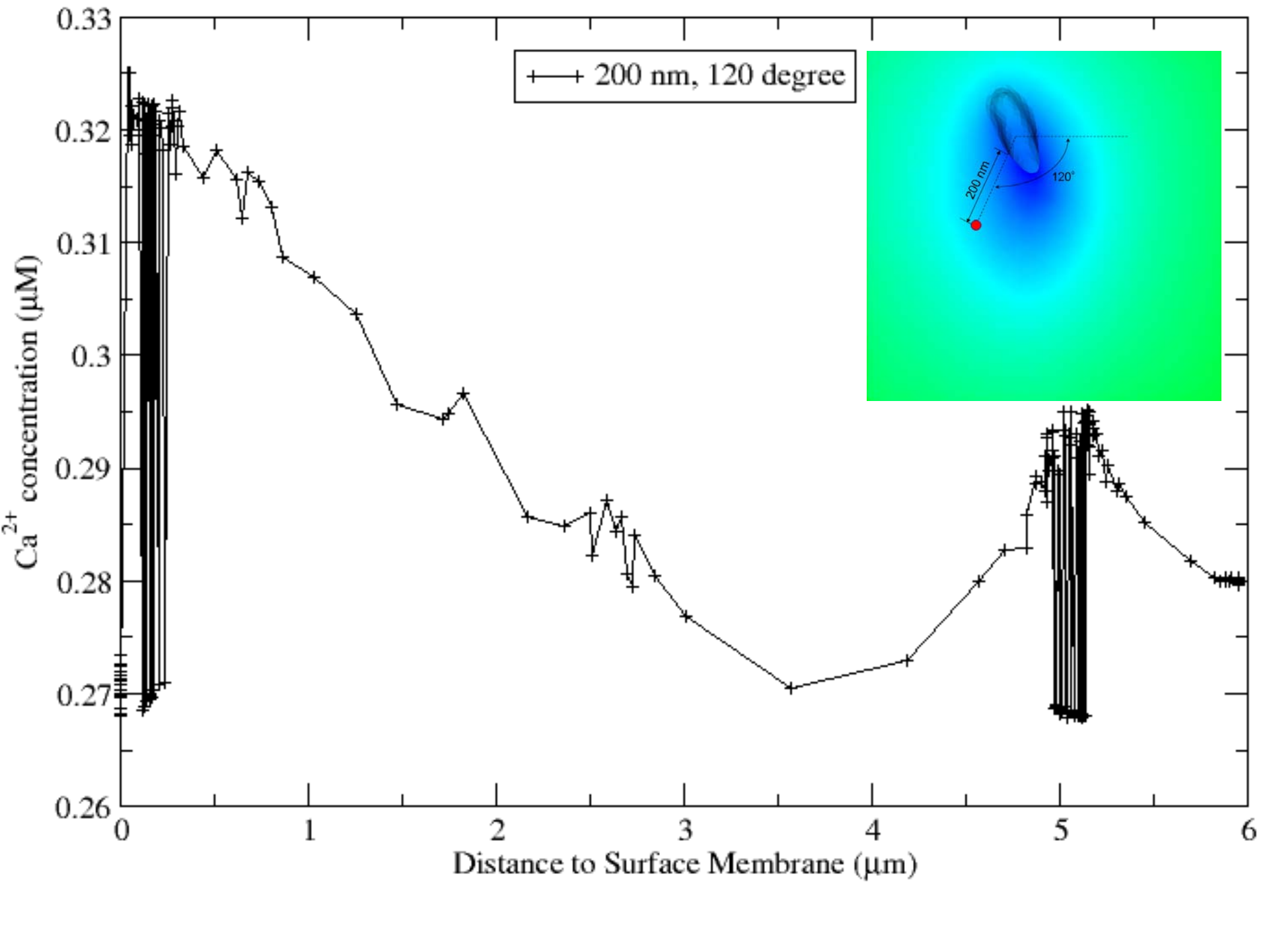
cd $HOME/smol2009

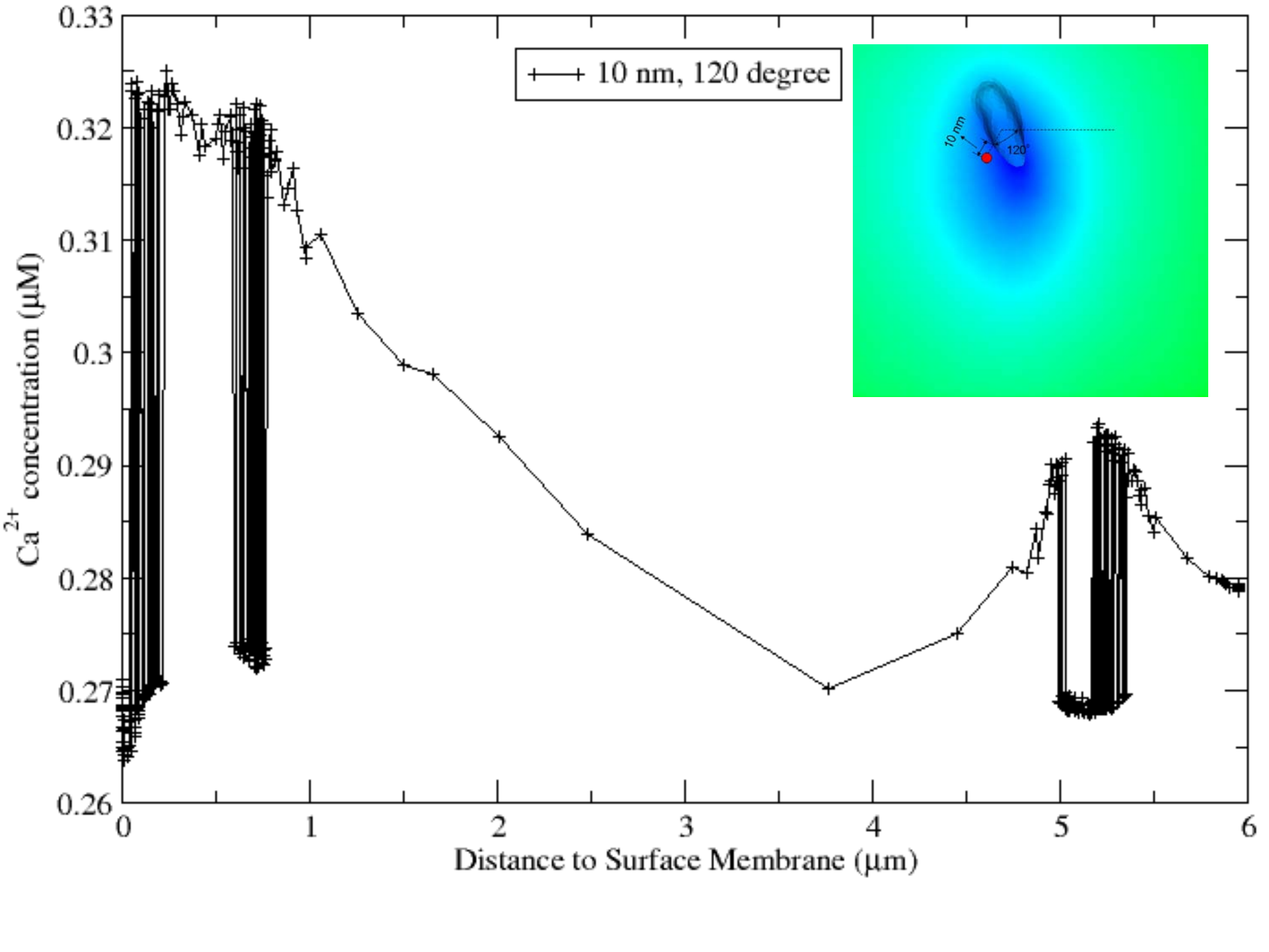
source bashrc

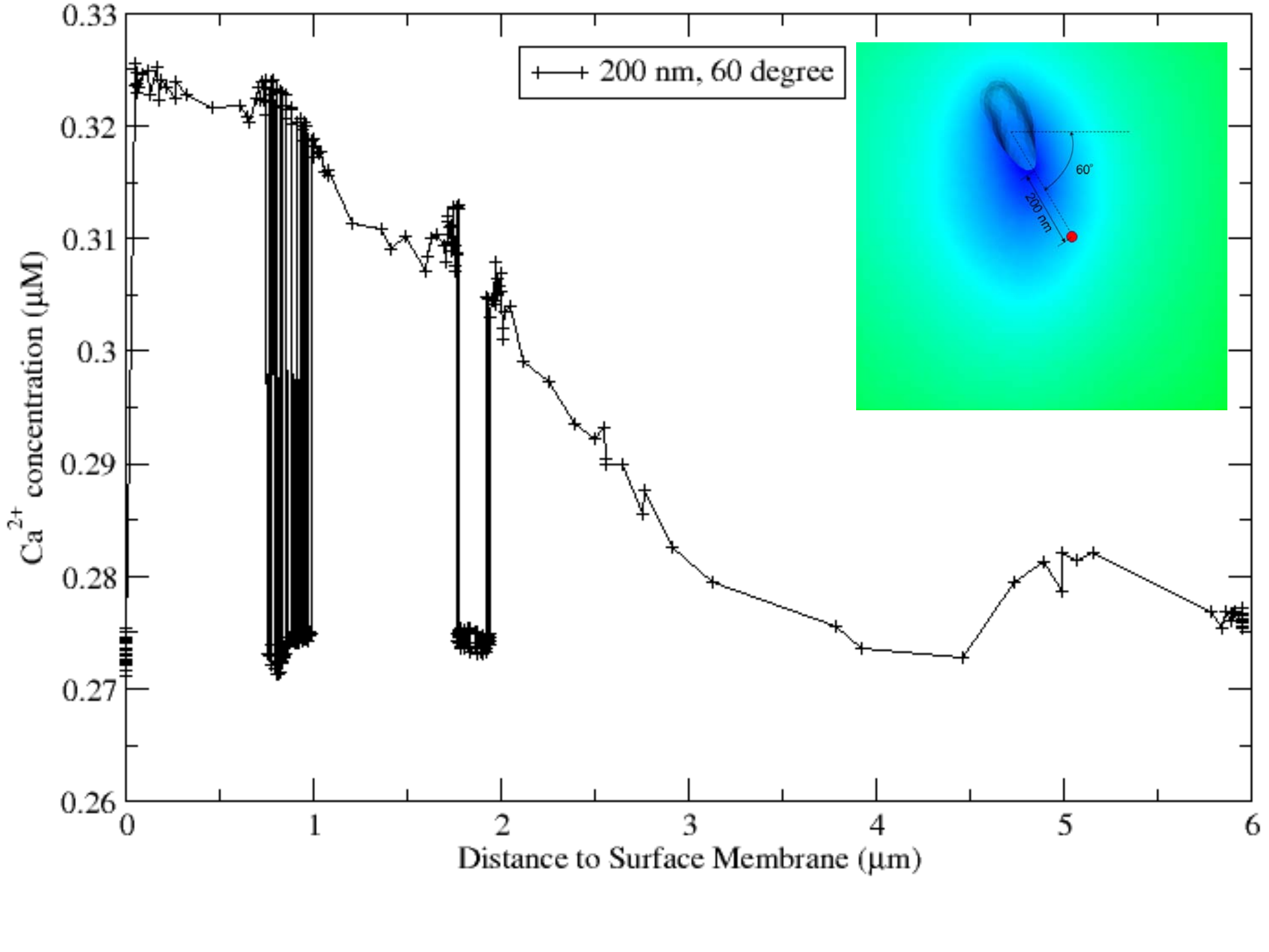
cd $HOME/smol2009/run/calcium/nofluo

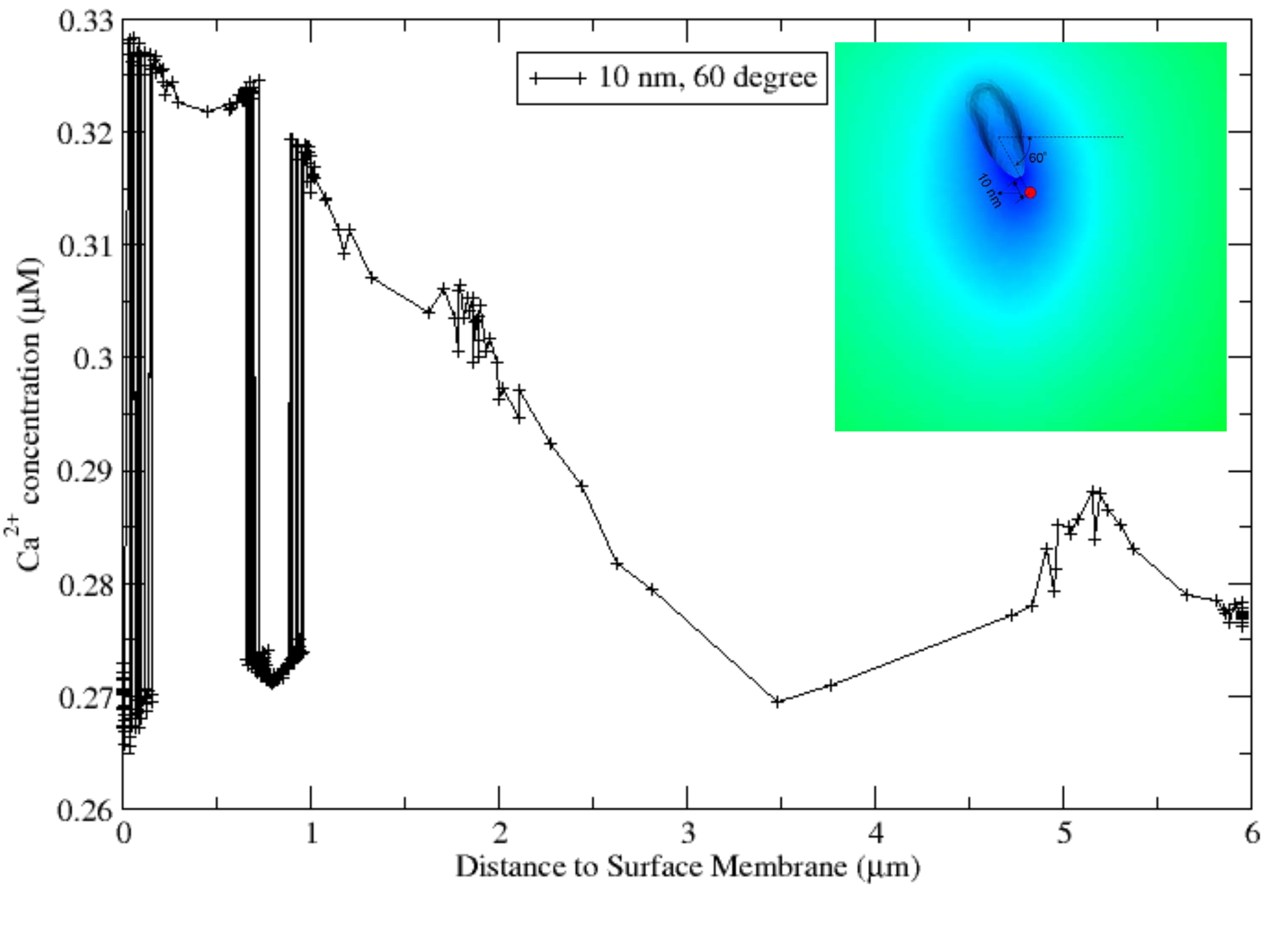
linuxMesa




200 nm, 120 degree
0.33
0.32
0.31
0.3
0.29
0.28
0.27
0.26
Ca^{2+} concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)
200 nm
120°


10 nm, 120 degree
10 nm
120°
0.33
0.32
0.31
0.3
0.29
0.28
0.27
0.26
Ca^{2+} concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)


200 nm, 60 degree
60°
200 nm
0.33
0.32
0.31
0.3
0.29
0.28
0.27
0.26
Ca2+ concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)


10 nm, 60 degree
60°
10 nm
0.33
0.32
0.31
0.3
0.29
0.28
0.27
0.26
Ca2+ concentration (μM)
0
1
2
3
4
5
6
Distance to Surface Membrane (μm)

Additional reading materials

1. http://en.wikipedia.org/wiki/Diffusion
2. Berg, H C. *Random Walks in Biology*. Princeton: Princeton Univ. Press, 1993
3. advanced diffusion materials:

http://www.ks.uiuc.edu/Services/Class/PHYS498NSM/

4. Adaptive Multilevel Finite Element Solution of the Poisson-Boltzmann Equation I: Algorithms and Examples. *J. Comput. Chem.*, 21 (2000), pp. 1319-1342.
5. Finite Element Solution of the Steady-State Smoluchowski Equation for Rate Constant Calculations. *Biophysical Journal,* 86 (2004), pp. 2017-2029.
6. Continuum Diffusion Reaction Rate Calculations of Wild-Type and Mutant Mouse Acetylcholinesterase: Adaptive Finite Element Analysis. *Biophysical Journal,* 87 (2004), pp.1558-1566.
7. Tetrameric Mouse Acetylcholinesterase: Continuum Diffusion Rate Calculations by Solving the Steady-State Smoluchowski Equation Using Finite Element Methods. *Biophysical Journal,* 88 (2005), pp. 1659-1665.
8. Finite Element Analysis of the Time-Dependent Smoluchowski Equation for Acetylcholinesterase Reaction Rate Calculations. Biophys. J., 92(2007), pp. 3397-3406
9. Diffusional Channeling in the Sulfate Activating Complex: Combined Continuum Modeling and Coarse-grained Brownian Dynamics Studies. *Biophys. J.,* 95(2008), pp. 4659-4667