

## Organization of MIRDcell V2.0 Graphical User Interface

- **Source Radiation**
  - *Predefined MIRD Radionuclide*
    - $\beta$  Full Energy Spectrum
    - $\beta$  Average Energy Spectrum
  - *Monoenergetic Particle Emitter*
  - *User Created Radionuclide*
    - Add Radiation
    - Confirm List of Radiations
  - *Input Data for Calculation*
- **Cell Source/Target**
- **Radiobiological Parameters**
- **Multicellular Geometry**
  - *1-D Cell Pair*
    - Distance between cells
  - *2-D Colony*
    - 2-D Colony
      - Cell Geometry
        - Number of cells
        - Distance between cells
        - Shape (Dimensions)
          - Circle (specify radius)
          - Rectangle (specify length and width)
          - Ellipse (specify short and long axis)
      - Cell Labeling
        - Labeling method
          - Uniform
          - Lognormal (specify sigma)
          - Normal (specify sigma)
        - Mean activity per cell (all cells)
        - Time-integrated activity coefficient ( $\bar{a}$ )
        - Number of cells labeled
        - Percentage of cells that are labeled
    - Activity Distribution
    - Surviving Fraction
      - SF labeled cells versus mean dose to labeled cells
      - SF unlabeled cells versus mean dose to unlabeled cells
      - SF all cells versus mean dose to all cells
  - *3-D Cluster*
    - 3-D Cluster
      - Cell Geometry
        - Number of cells
        - Distance between cells
        - Shape (Dimensions)
          - Sphere (specify radius)
          - Rod (specify length and width)
          - Ellipsoid (specify short and long axis)
      - Cell Labeling
        - Labeling method
          - Uniform
          - Lognormal (specify sigma)
          - Normal (specify sigma)
        - Mean activity per cell (all cells)
        - Time-integrated activity coefficient ( $\bar{a}$ )
        - Number of cells labeled
        - Percentage of cells that are labeled
      - Activity Distribution
      - Surviving Fraction
        - SF labeled cells versus mean dose to labeled cells
        - SF unlabeled cells versus mean dose to unlabeled cells
        - SF all cells versus mean dose to all cells
- **Output**

## Computer Specifications

### **Hardware requirements:**

MIRDcell V2.0 must be run on a computer with substantial computational power and with Internet access. It will freeze on PC's equipped with Intel Core 2 Duo or lower CPU's. Tests were conducted with MIRDcell V2.0 running on the following computer systems:

1. Dell Latitude E5430 laptop PC equipped with an Intel Core i7-3520M CPU @ 2.9 GHz (2 cores/4 threads), and 8GB DDR3 RAM.
2. Dell Inspiron 1764 laptop PC equipped with an Intel Core i5-M430 @ 2.27 GHz (2 cores/4 threads), and 4GB DDR3 RAM.
3. Dell Optiplex 990 desktop PC equipped with an Intel Core i7-2600 CPU @ 3.4 GHz (4 cores/8 threads), and 16GB DDR3 RAM.

*Users are cautioned to use a personal computer with at least these levels of hardware sophistication. The Optiplex 990 desktop performance was substantially superior.*

### **Software requirements:**

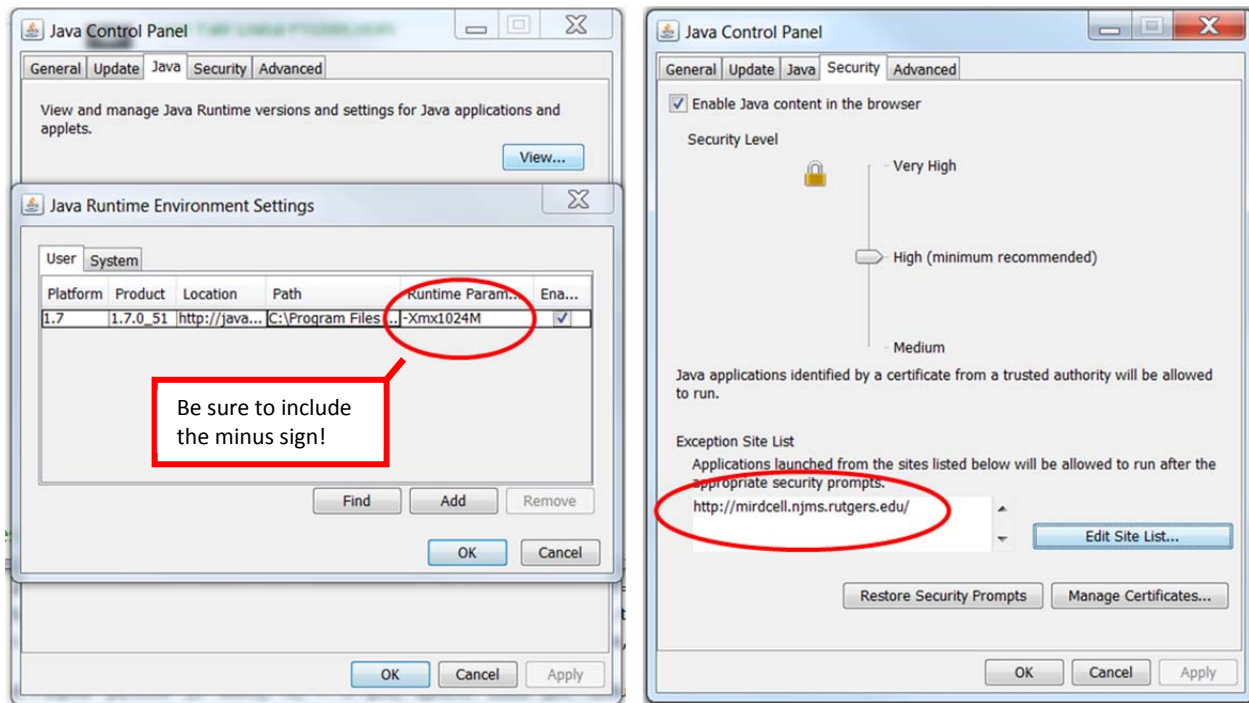
MIRDcell V2.0 was tested on the following software environment.

1. *Operating system:* 64 bit Windows 7, USA and Chinese versions
2. *Web browser:* Internet Explorer Version 10.0.9200.16736
3. *Java:* **32 bit** Java Platform Version 7 Update 51
4. *Java (32-bit) control panel (in Windows control panel):*
  - a. Security tab
    - i. Add <http://mirdcell.njms.rutgers.edu> as an Exception site
  - b. Java Tab – View – Java Runtime Environment Settings
    - i. Runtime parameter = `-Xmx1024MB` (be sure to include the dash)

The `-Xmx1024MB` parameter allocates 1GB of RAM for Java. This overrides the default memory allocation of 128MB. This increase is necessary because MIRDcell V2.0 may freeze when memory allocation is not sufficient to handle calculations for multicellular clusters that contain a large number of cells.

No tests have been conducted for 64 bit Java.

**SCREEN SHOTS OF THE JAVA (32-bit) CONTROL PANEL SETTINGS ARE ON THE FOLLOWING PAGE:**



Benchmark computation times (t = hr:min:s) for the computers are as follows:

- 1) Dell Latitude E5430
  - a.  $^{210}\text{Po}$ ,  $R_C = 5 \mu\text{m}$ , sphere 100  $\mu\text{m}$  radius, 100% labeling, 4169 cells, t = 00:00:35
  - b.  $^{210}\text{Po}$ ,  $R_C = 5 \mu\text{m}$ , sphere 200  $\mu\text{m}$  radius, 100% labeling, 33401 cells, t = 00:01:30
  - c.  $^{210}\text{Po}$ ,  $R_C = 5 \mu\text{m}$ , sphere 200  $\mu\text{m}$  radius, 1% labeling, 33401 cells, t = 00:00:50
  - d.  $^{131}\text{I}$  (avg  $\beta$ ),  $R_C = 5 \mu\text{m}$ , sphere 200  $\mu\text{m}$  radius, 1% labeling, 33401 cells, t = 00:01:40
  - e.  $^{131}\text{I}$  (full  $\beta$ ),  $R_C = 5 \mu\text{m}$ , sphere 200  $\mu\text{m}$  radius, 100% labeling, 33401 cells, t = 00:01:01
- 2) Dell Optiplex 990
  - a.  $^{210}\text{Po}$ ,  $R_C = 5 \mu\text{m}$ , sphere 100  $\mu\text{m}$  radius, 100% labeling, 4169 cells, t = 00:00:15
  - b.  $^{210}\text{Po}$ ,  $R_C = 5 \mu\text{m}$ , sphere 200  $\mu\text{m}$  radius, 100% labeling, 33401 cells, t = 00:00:40
  - c. alpha particle (5 MeV),  $R_C = 5 \mu\text{m}$ , sphere 1000  $\mu\text{m}$  radius, 0.1% labeling, 4187857 cells, t = 00:15:00
  - d. alpha particle (5 MeV),  $R_C = 5 \mu\text{m}$ , sphere 1000  $\mu\text{m}$  radius, 1% labeling, 4187857 cells, t = 00:30:00
- 3) Dell Inspiron 1764
  - a.  $^{210}\text{Po}$ ,  $R_C = 5 \mu\text{m}$ , sphere 200  $\mu\text{m}$  radius, 100% labeling, 33401 cells, t = 00:01:31
  - b. alpha particle (5 MeV),  $R_C = 5 \mu\text{m}$ , sphere 1000  $\mu\text{m}$  radius, 0.1% labeling, 4187857 cells, t = 00:44:00

These tests suggest that computations involving up to  $\sim 10^6$  cells can be achieved in reasonable times on the hardware and software platforms tested. The computations above in item 2d with  $4 \times 10^6$  cells result in just over 1 GB of RAM usage by Java. Users should be aware that computation times depend on many factors, especially range of radiations emitted, number of cells, and percentage of cells that are labeled.

## Worked Examples

### 1. Cells in Suspension (no significant cross-dose)

Published data can be used to demonstrate the capacity of MIRDcell V2.0 to simulate the response of cells with  $^{125}\text{I}$  incorporated into DNA in the cell nucleus (1). Briefly, Chinese hamster V79 cells were suspended in culture medium containing various concentrations of  $^{125}\text{I}$ -iododeoxycytidine ( $^{125}\text{IdC}$ ) for 18 h, washed, and seeded into culture dishes to measure clonogenic cell survival. The radii of the cell and cell nucleus were measured to be 5 and 4  $\mu\text{m}$ , respectively. Cellular activity was measured and virtually all of the activity was localized in the cell nucleus. The cellular activity corresponding to treatment with the highest concentration of  $^{125}\text{IdC}$  was approximately 3.2 mBq per cell. The mean uptake of the radiochemical was linearly dependent on time, whereas the clearance was exponential with an effective half-time of 12 h. This yields a time integrated activity coefficient (formerly known as residence time (2)) for the incubation and colony forming periods of 26.3 h. The plot of surviving fraction as a function of cellular activity was monoexponential. In this example, assume that the cellular cross-dose is negligible during all stages of the experiment, so only the cellular self-dose needs to be considered. Use MIRDcell V2.0 to plot a cell survival curve.

- Click on the source radiation tab. Select I-125 from the drop-down list and click “ $\beta$  average energy spectrum”. Note that the Input Data box filled in with the radiation data.

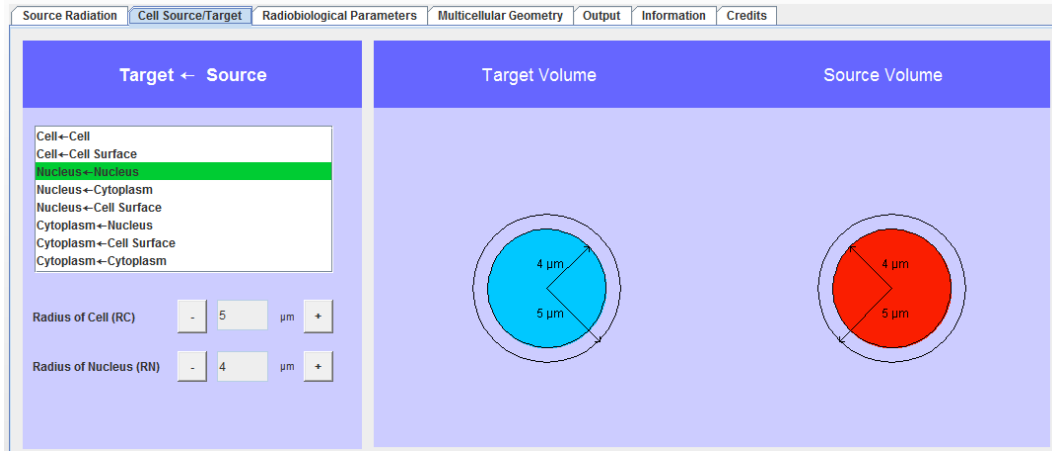
The screenshot displays the MIRDcell V2.0 software interface with the 'Source Radiation' tab selected. The interface is divided into four main sections:

- Predefined MIRD Radionuclide:** Features two radio buttons: 'Full Energy Spectrum' (unselected) and 'Average Energy Spectrum' (selected). A dropdown menu for 'Radionuclide' is open, showing a list of isotopes with 'I-125' highlighted.
- Monoenergetic Particle Emitter:** Features two radio buttons: 'Alpha Particle' (unselected) and 'Electron' (selected). Below are input fields for 'Yield / Decay' and 'Energy (MeV)', both currently empty.
- User Created Radionuclide:** Features two radio buttons: 'Retrieve' (unselected) and 'Create' (unselected). It includes an 'Open' button, a 'Name' input field, a 'Help' button, a 'Choose radiation' dropdown, 'Yield / Decay' and 'Energy (MeV)' input fields, and buttons for 'Add Radiation', 'Confirm List of Radiations', and 'Save Radionuclide (to your disk)'.
- Input Data for Calculation:** A text area displaying the output file 'OutPutI-125.RAD for I-125' with the following content:

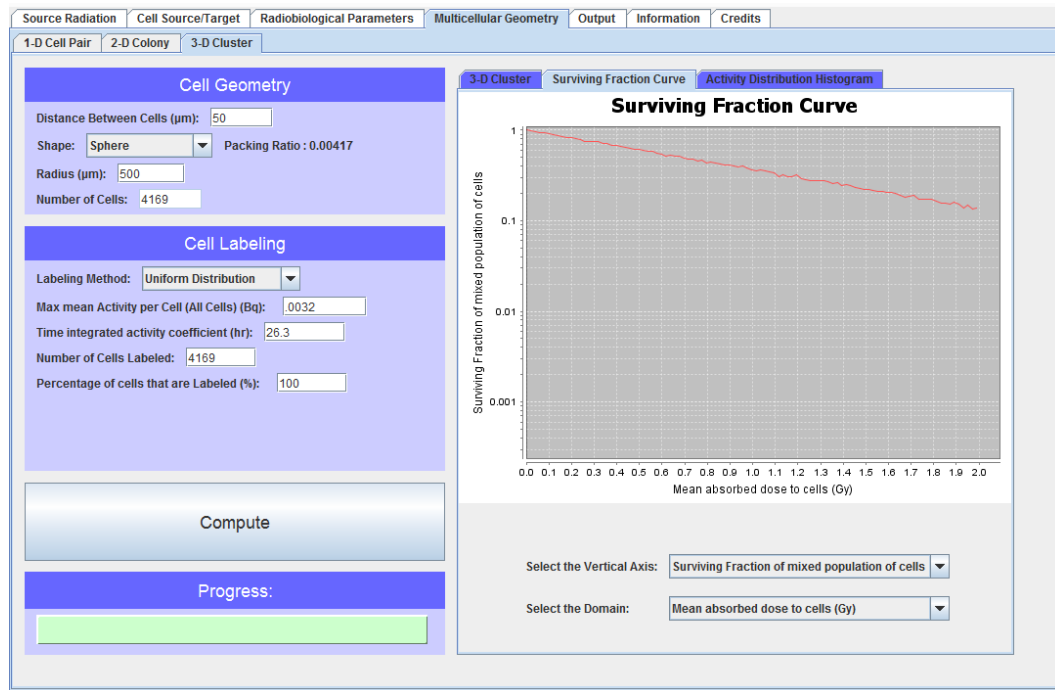
```
Output File OutPutI-125.RAD for I-125
I-125 59.400d 69
T1/2 = 59.400d Decay Mode: EC
Radiations of each type listed in increasing energy
Number of photon radiations: 50
Number of monoenergetic electron radiations: 19
ICODE Y (int) E(MeV) Mnemonic
START RADIATION RECORDS
2 2.49659E+01 1.36106E-05 X
2 1.69993E-04 7.62079E-05 X
2 2.60776E-08 2.78500E-04 X
2 6.81913E-06 2.96000E-04 X
```

A 'Reset' button is located at the bottom of this section.

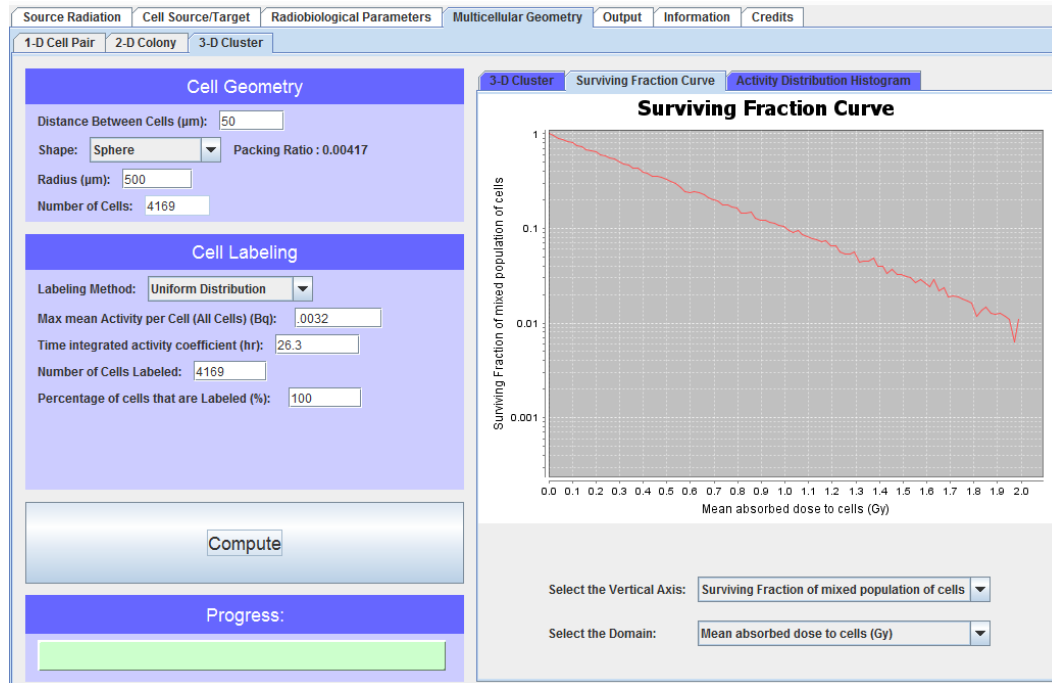
- b. Click on the Cell Source/Target tab. Select Nucleus ← Nucleus. Click on + to increase radius of cell nucleus to 4 μm.



- c. Since one has been instructed to assume that the cross-dose is negligible, create geometric conditions that will satisfy that requirement. Click the Multicellular Geometry tab and then click the 3-D Cluster tab. Increase distance between cells to 50 μm to simulate the suspension culture. The large distance relative to the range of the short-range conversion electrons emitted by  $^{125}\text{I}$  will result in a negligible cross-dose. From the drop-down list of Shapes, select Sphere. Enter a radius that will contain enough cells to enable simulation of at least two logs of cell kill – the amount observed in the experimental data (1). Start with a 500 μm radius. Select Labeling Method to be Uniform Distribution. Enter the Maximum mean Activity per Cell = 3.2 mBq = 0.0032 Bq. Enter the Time integrated activity coefficient = 26.3 h. Enter Percentage of cells that are Labeled = 100%. Click Compute. Click the Surviving Fraction Curve tab.



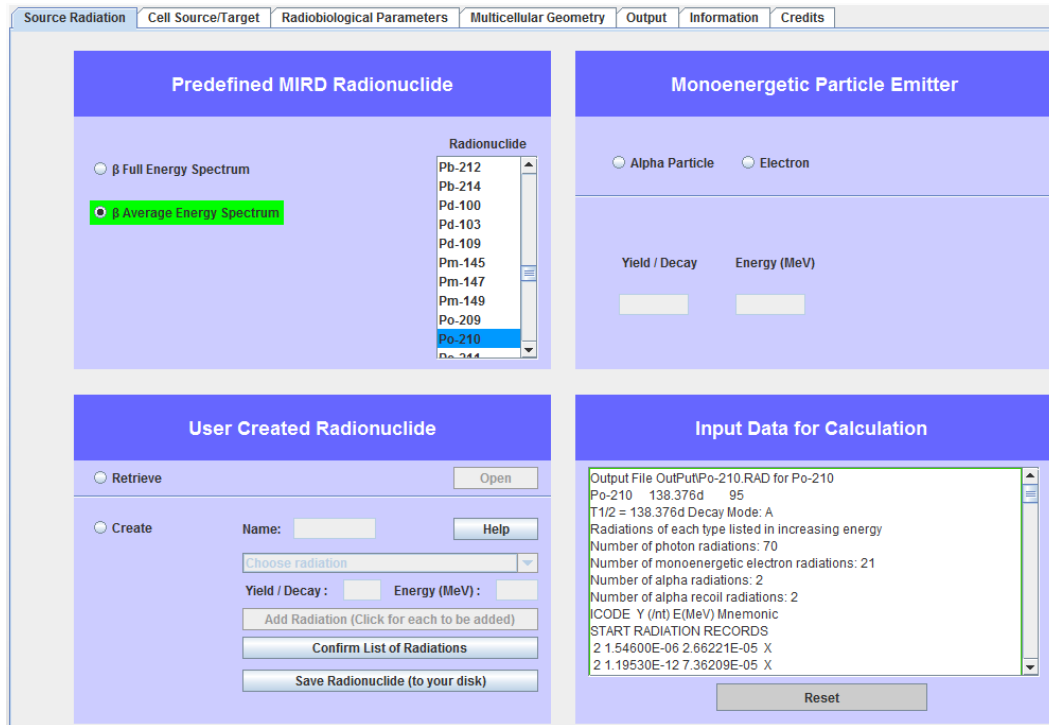
- d. Compare resulting curve of Surviving Fraction mixed population of cells (in this case all cells are labeled so mixed = labeled) with Figure 5 of Ref. (1). Note that there is a poor correspondence with the absorbed dose that causes 37% survival ( $D_{37}$ ). This is because the default values for Radiobiological Parameters were used. Click the Radiobiological Parameters tab (GUI not shown). Set the radiobiological parameters to the values that were obtained in Ref. (1):  $\alpha_{\text{self}} = 2.3 \text{ Gy}^{-1}$ ,  $\beta_{\text{self}} = 0 \text{ Gy}^{-2}$ ,  $\alpha_{\text{cross}} = 2.3 \text{ Gy}^{-1}$ ,  $\beta_{\text{cross}} = 0 \text{ Gy}^{-2}$ . Click the Multicellular Geometry tab. Click Compute. Note that the simulated survival curve now matches the published survival curve in Figure 5 of Ref. (1).



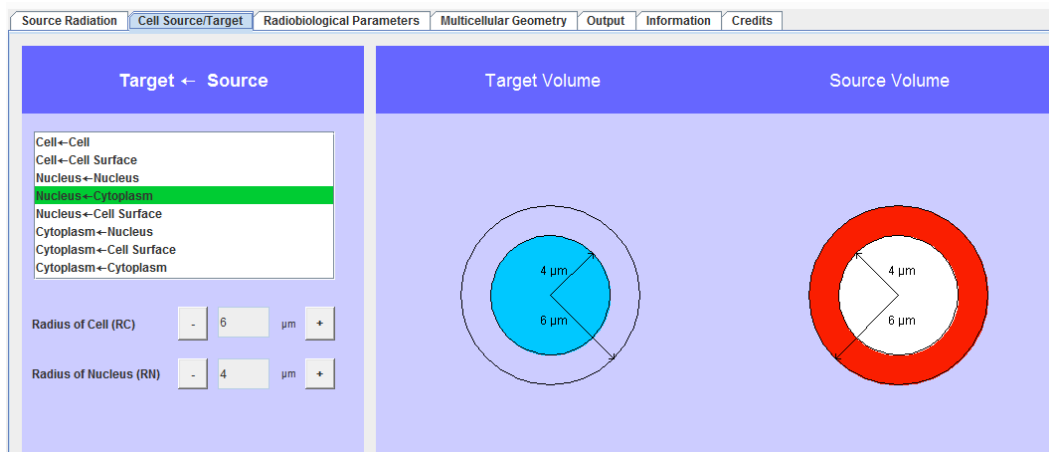
## 2. 3D Multicellular Cluster of Cultured Cells

Consider using MIRDcell V2.0 to predict the response of a multicellular cluster of cells labeled with the alpha particle emitter,  $^{210}\text{Po}$ . The experimental data of Neti et al. (3) are analyzed as follows. Modeling is conducted analogous to that described in Howell et al. (4), except that the size of the cluster is decreased here to reduce computation time. The experimental cluster consists of cells, labeled with  $^{210}\text{Po}$ , and tightly packed into a pellet at the bottom of a microcentrifuge tube. Cell clusters, containing various quantities of radioactivity, were maintained in these tubes for to accumulate decays. The clusters were then dismantled, serial dilutions of the cells were seeded into culture dishes for the colony forming assay. The surviving fraction of initially seeded cells compared to controls was calculated and plotted as a function of mean activity per cell. Measurements of the diameters of the cell and cell nucleus yielded averages of 12 and 8 μm, respectively. In this example, the activity will be assumed to be distributed in the cytoplasm. As in Ref. (4), the cells will be constrained to a conical volume with a height equal to the diameter of the top surface. Here only a portion of the cells (68,883 out of  $4 \times 10^6$  cells) will be modeled to reduce CPU time and stay within the 1024 MB memory limit for 32 bit Java. Tests show that the 1024 MB setting in Java can accommodate up to about  $10^6$  cells. As in Ref. (3), a lognormal distribution of activity will be selected with a shape factor of 2.0.

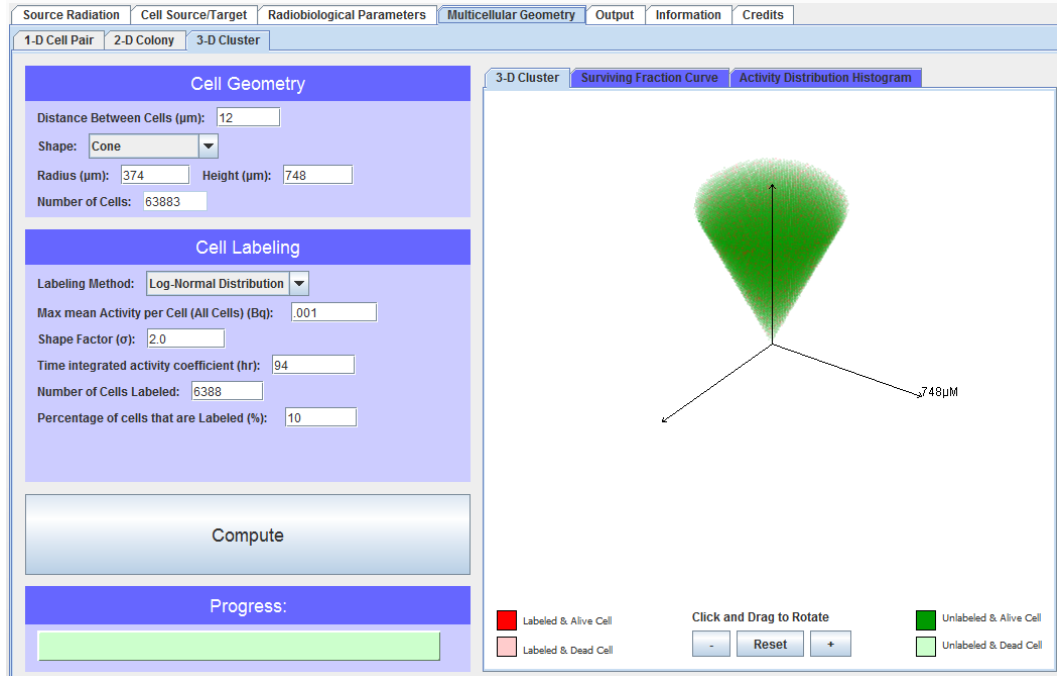
- a. Click on the source radiation tab. Select Po-210 from the drop-down list and click “β average energy spectrum”. Note that the Input Data box filled in with the appropriate radiation data.



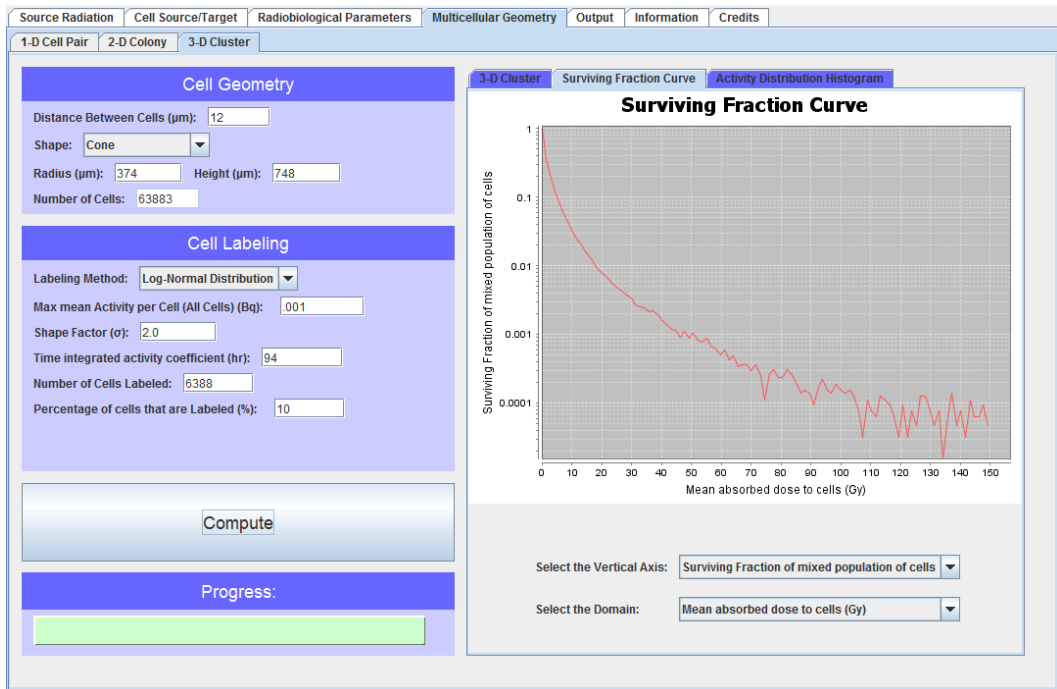
- b. Click on the Cell Source/Target tab. Select Nucleus ← Cytoplasm. Click on + to increase radius of cell nucleus to 4 μm. Click on + to increase radius of cell to 6 μm.



- c. Set the Radiobiological Parameters to (3):  $\alpha_{\text{self}} = 1.54 \text{ Gy}^{-1}$ ,  $\beta_{\text{self}} = 0 \text{ Gy}^{-2}$ ,  $\alpha_{\text{cross}} = 1.54 \text{ Gy}^{-1}$ ,  $\beta_{\text{cross}} = 0 \text{ Gy}^{-2}$ . Click the Multicellular Geometry tab and then click the 3-D colony tab. From the drop-down list of Shapes, select Cone. Enter a radius of 374 μm radius and 748 μm height. Select Labeling Method to be Lognormal Distribution and the Shape Factor = 2.0. Enter the Maximum mean Activity per Cell = 0.001 Bq. Enter the Time integrated activity coefficient = 94 h. Enter Percentage of cells that are Labeled = 10%. Click Compute.

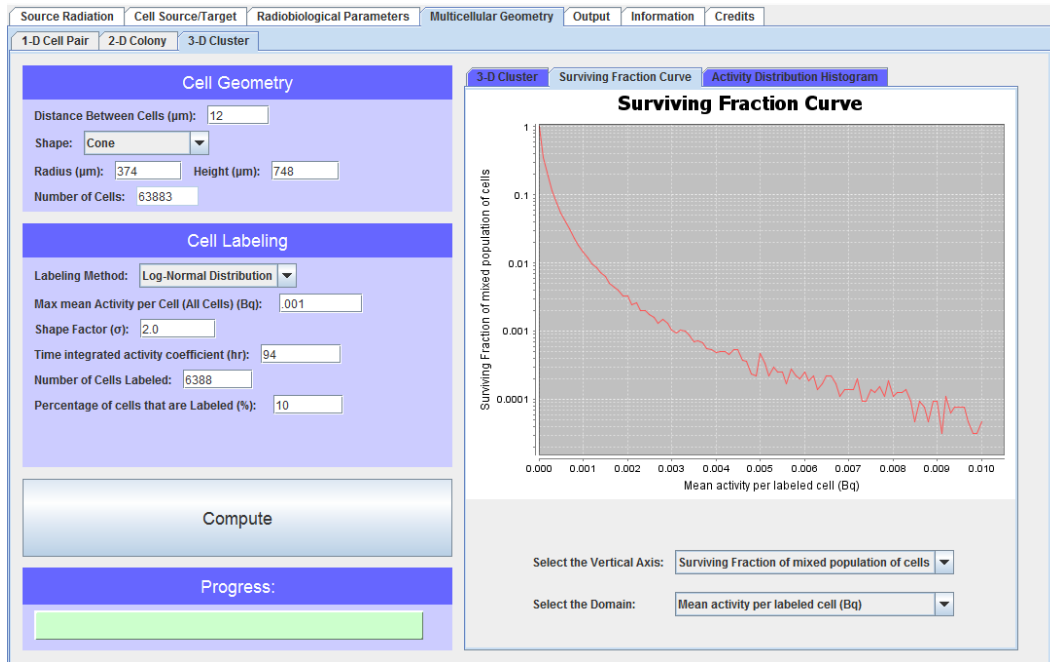


d. Click the Surviving Fraction Curve tab.

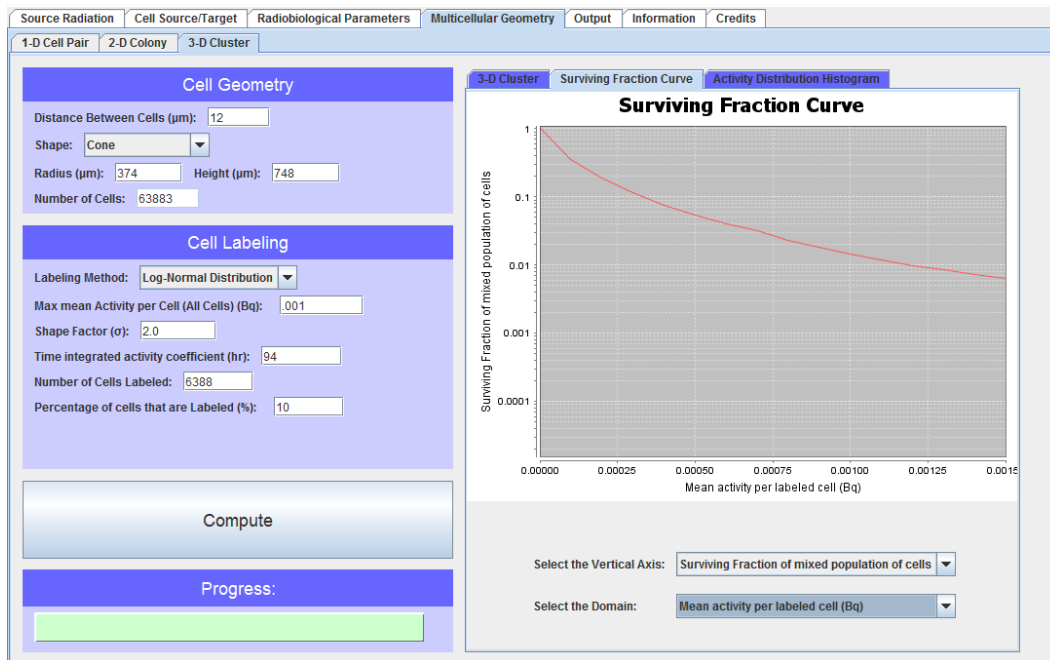




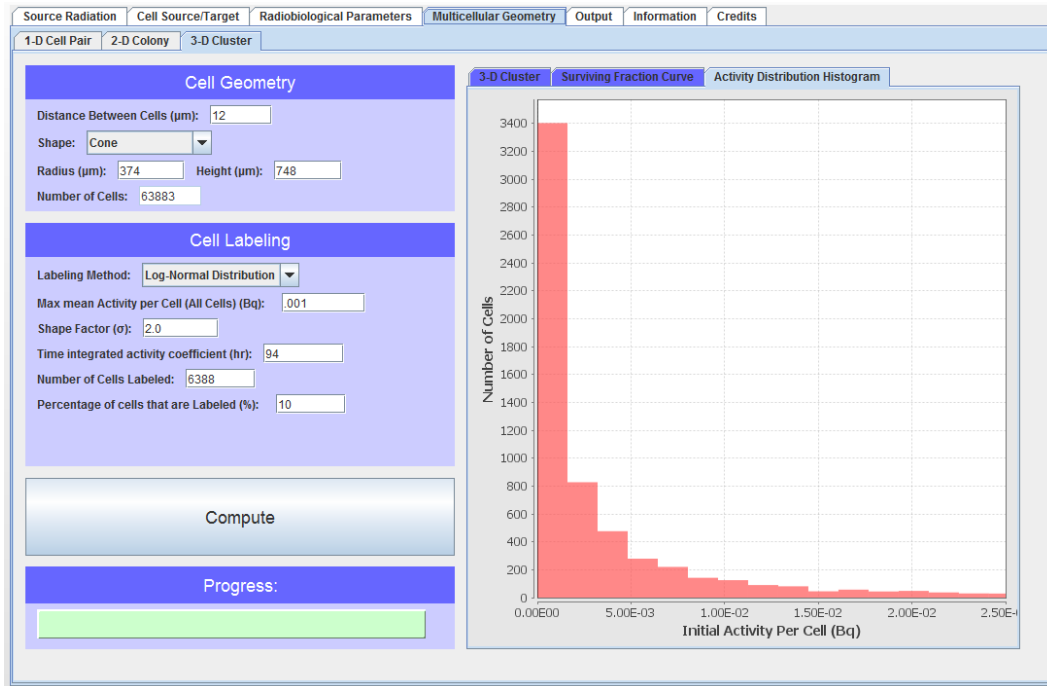
- e. Select the Domain to be Mean Activity per Labeled Cell.



- f. Right click on horizontal axis scale. Click on Properties tab. Click on Plot. In Other box, Click on Range. Uncheck Auto-adjust range. Change Maximum range value to 0.0015. Click OK. The resulting plot is a reasonable match with Figure 3 of Neti et al. (3).



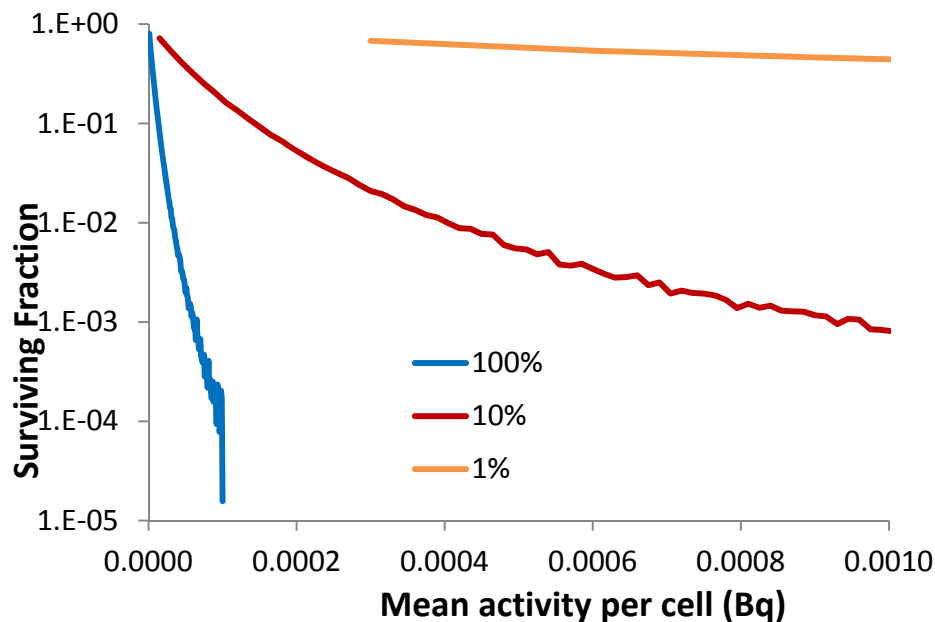
- g. Click the Activity Distribution Histogram tab. Right click on horizontal axis scale. Click on Properties tab. Click on Plot. In Other box, Click on Range. Uncheck Auto-adjust range. Change Maximum range value to 0.025. Click OK. The lognormal distribution is apparent.



- h. Click the Output Tab. Highlight data in columns of data in left box. Right click and copy.

|  | Distance<br>µm | S(C←C)<br>Gy/Bq.s | S(C←CS)<br>Gy/Bq.s | S(N←N)<br>Gy/Bq.s | S(N←Cy)<br>Gy/Bq.s | S(N←CS)<br>Gy/Bq.s | S(Cy←N)<br>Gy/Bq.s | S(Cy←CS)<br>Gy/Bq.s | S(Cy←Cy)<br>Gy/Bq.s |
|--|----------------|-------------------|--------------------|-------------------|--------------------|--------------------|--------------------|---------------------|---------------------|
| Shape Factor (σ) =                           | 2.0            |                   |                    |                   |                    |                    |                    |                     |                     |
| Maximum mean activity per cell (Bq) =        | .001           |                   |                    |                   |                    |                    |                    |                     |                     |
| Time integrated activity coefficient (hr) =  | 94             |                   |                    |                   |                    |                    |                    |                     |                     |
| MAC = mean activity per cell                 |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MDC = mean absorbed dose to cells            |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MALC = mean activity per labeled cell        |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MDLC = mean absorbed dose to labeled cells   |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MDUC = mean absorbed dose to unlabeled cells |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MAC(Bq)                                      |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MDC(Gy)                                      |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MALC(Bq)                                     |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MDLC(Gy)                                     |                |                   |                    |                   |                    |                    |                    |                     |                     |
| MDUC(Gy)                                     |                |                   |                    |                   |                    |                    |                    |                     |                     |
| SF(labeled)                                  |                |                   |                    |                   |                    |                    |                    |                     |                     |
| SF(unlabeled)                                |                |                   |                    |                   |                    |                    |                    |                     |                     |
| 1.00E-05                                     | 1.43E00        | 1.00E-04          | 2.96E00            | 1.26E00           | 2.11E-01           |                    |                    |                     |                     |
| 2.00E-05                                     | 2.87E00        | 2.00E-04          | 5.93E00            | 2.52E00           | 4.22E-02           |                    |                    |                     |                     |
| 3.00E-05                                     | 4.30E00        | 3.00E-04          | 8.89E00            | 3.79E00           | 4.82E-02           |                    |                    |                     |                     |
| 4.00E-05                                     | 5.73E00        | 4.00E-04          | 1.19E01            | 5.05E00           | 2.71E-02           |                    |                    |                     |                     |
| 5.00E-05                                     | 7.16E00        | 5.00E-04          | 1.48E01            | 6.31E00           | 1.80E-02           |                    |                    |                     |                     |
|  | 733            | 5.56E-16          | 5.56E-16           | 5.56E-16          | 5.56E-16           | 5.56E-16           | 5.56E-16           | 5.56E-16            | 5.56E-16            |
|  | 734            | 5.54E-16          | 5.54E-16           | 5.54E-16          | 5.54E-16           | 5.54E-16           | 5.54E-16           | 5.54E-16            | 5.54E-16            |
|  | 735            | 5.53E-16          | 5.53E-16           | 5.53E-16          | 5.53E-16           | 5.53E-16           | 5.53E-16           | 5.53E-16            | 5.53E-16            |
|  | 736            | 5.51E-16          | 5.51E-16           | 5.51E-16          | 5.51E-16           | 5.51E-16           | 5.51E-16           | 5.51E-16            | 5.51E-16            |
|  | 737            | 5.50E-16          | 5.50E-16           | 5.50E-16          | 5.50E-16           | 5.50E-16           | 5.50E-16           | 5.50E-16            | 5.50E-16            |
|  | 738            | 5.48E-16          | 5.48E-16           | 5.48E-16          | 5.48E-16           | 5.48E-16           | 5.48E-16           | 5.48E-16            | 5.48E-16            |
|  | 739            | 5.47E-16          | 5.47E-16           | 5.47E-16          | 5.47E-16           | 5.47E-16           | 5.47E-16           | 5.47E-16            | 5.47E-16            |
|  | 740            | 5.45E-16          | 5.45E-16           | 5.45E-16          | 5.45E-16           | 5.45E-16           | 5.45E-16           | 5.45E-16            | 5.45E-16            |
|  | 741            | 5.44E-16          | 5.44E-16           | 5.44E-16          | 5.44E-16           | 5.44E-16           | 5.44E-16           | 5.44E-16            | 5.44E-16            |
|  | 742            | 5.42E-16          | 5.42E-16           | 5.42E-16          | 5.42E-16           | 5.42E-16           | 5.42E-16           | 5.42E-16            | 5.42E-16            |
|  | 743            | 5.41E-16          | 5.41E-16           | 5.41E-16          | 5.41E-16           | 5.41E-16           | 5.41E-16           | 5.41E-16            | 5.41E-16            |
|  | 744            | 5.40E-16          | 5.40E-16           | 5.40E-16          | 5.40E-16           | 5.40E-16           | 5.40E-16           | 5.40E-16            | 5.40E-16            |
|  | 745            | 5.38E-16          | 5.38E-16           | 5.38E-16          | 5.38E-16           | 5.38E-16           | 5.38E-16           | 5.38E-16            | 5.38E-16            |
|  | 746            | 5.37E-16          | 5.37E-16           | 5.37E-16          | 5.37E-16           | 5.37E-16           | 5.37E-16           | 5.37E-16            | 5.37E-16            |
|  | 747            | 5.35E-16          | 5.35E-16           | 5.35E-16          | 5.35E-16           | 5.35E-16           | 5.35E-16           | 5.35E-16            | 5.35E-16            |
|  | 748            | 5.34E-16          | 5.34E-16           | 5.34E-16          | 5.34E-16           | 5.34E-16           | 5.34E-16           | 5.34E-16            | 5.34E-16            |

- i. Paste data into Excel 2010 using its Paste - Text Import Wizard. Repeat procedure for 100% labeling and 1% labeling and paste into Excel files. Use Excel to plot surviving fraction versus mean activity per cell (MAC) as shown below. This demonstrates the MIRDcell V2.0 export capability.

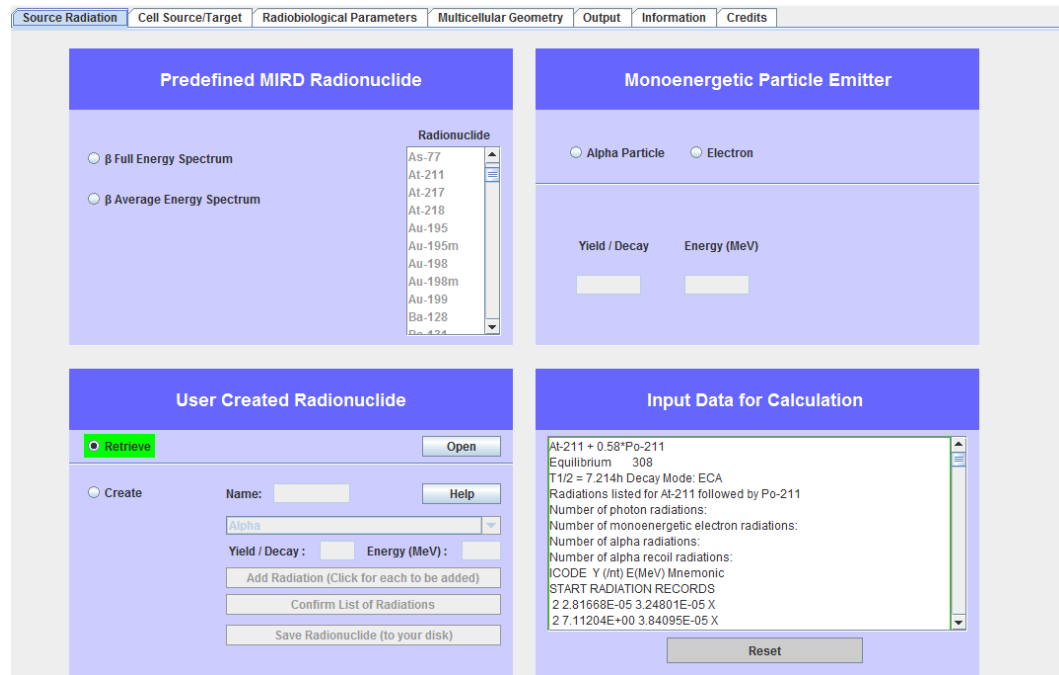


### 3. 3D Multicellular Clusters In Vivo. Analyses involving decay chains: $^{211}\text{At}$

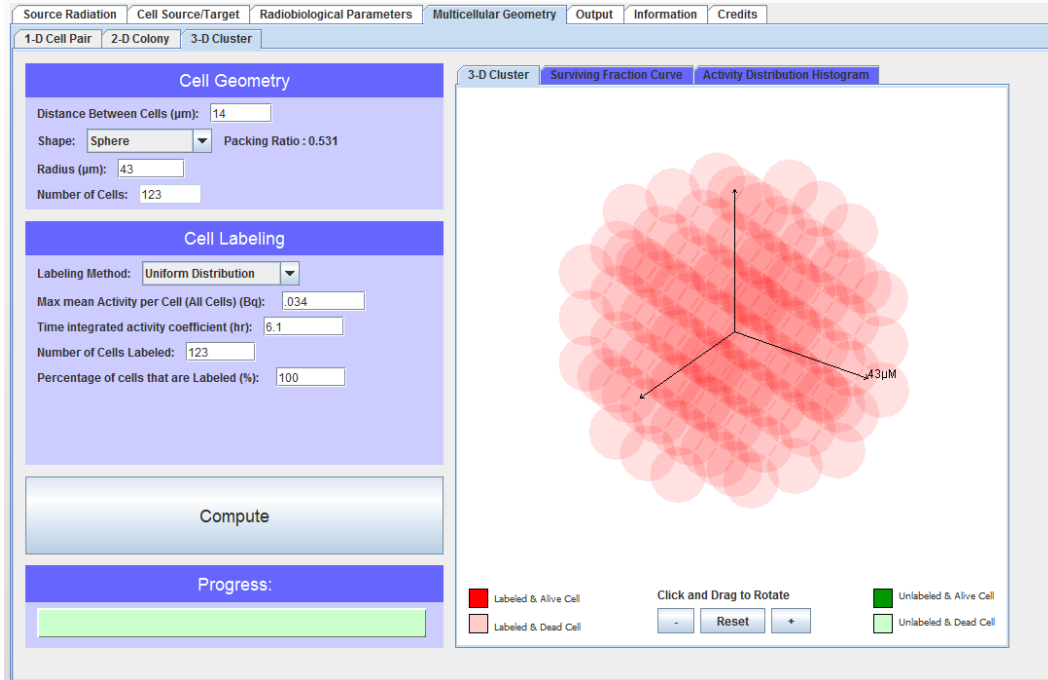
MIRDcell V2.0 can also be used to analyze data acquired at the cellular scale in vivo. Chouin et al. used their novel alpha camera to measure the cellular uptake of  $^{211}\text{At}$  in multicellular clusters of human ovarian cancer cells NIH:OVCAR-3 growing in the peritoneal cavity of mice (5). The  $D_{37}$  for these cells is 0.56 Gy ( $\alpha = 1.79 \text{ Gy}^{-1}$ ) when irradiated with alpha particles. Measurements were made for several cluster sizes; here the cluster with a radius of 42.8- $\mu\text{m}$  will be considered (modeled by a spheroid containing 123 cells). The cell and cell nuclei had average radii of 6.9 and 5.5  $\mu\text{m}$ , respectively. According to the second to last paragraph of the Results in Chouin et al. (5), "For 6-MBq injections, the activity per cell was constant from 1.5 h ( $\sim 0.027 \pm 0.010 \text{ Bq/cell}$ ) to 4 h ( $\sim 0.034 \pm 0.012 \text{ Bq/cell}$ ), then decreased slightly at 8 h ( $\sim 0.015 \pm 0.010 \text{ Bq/cell}$ )". Therefore, the maximum  $^{211}\text{At}$  uptake was 0.034 Bq/cell. The following paragraph in Chouin et al. (5) indicates that this activity delivers about 750 decays per cell. Therefore, the cellular time integrated activity coefficient, formerly known as the residence time,  $\tilde{a}$  can be approximated with  $\tilde{a} = \tilde{A}/A_0$ . The cumulated activity  $\tilde{A}$  is simply 750 decays = 750 Bq s and  $A_0 \sim 0.034 \text{ Bq}$ , therefore  $\tilde{a} = 6.1 \text{ hours}$ .

- a. The modeling process begins by first considering that  $^{211}\text{At}$  decays to its daughter  $^{211}\text{Po}$ , which decays in turn. If it is assumed that the parent and daughter are in equilibrium at all times, then radiations emitted by both parent and daughter need to be summed. Care must be taken to correct the  $^{211}\text{Po}$  radiation yields for the  $^{211}\text{At} \rightarrow ^{211}\text{Po}$  branching ratio of 0.582. This can be accomplished by clicking the  $\beta$  Average Energy Spectrum database button and selecting  $^{211}\text{At}$  from the list of Predefined Radionuclides on the Source Radiation tab. Copy the data in the Input Data for Calculation box and paste it into Excel. Repeat the process for  $^{211}\text{Po}$ . Multiply all  $^{211}\text{Po}$  yields by a factor of 0.582. Paste the corrected  $^{211}\text{Po}$  data into a text

file and then do the same for the  $^{211}\text{At}$  data. Be sure to add header and footer data and format all numbers to match those in single radionuclide files. The resulting text file can be retrieved using the button in the User Created Radionuclide box. **NOTE:** After writing this example, the combined  $^{211}\text{At}$  + daughters was made available in MIRDcell V2.0.12 in the radionuclide choices in the Average  $\beta$  Spectrum category. Nevertheless, the approach used above can be applied to any decay chain not present in the radionuclide choices.



- b. Click the Cell Source/Target tab and select Nucleus < Cell Surface and set the radii of the cell and cell nucleus to 7  $\mu\text{m}$  and 5  $\mu\text{m}$ , respectively. Click the Radiobiological Parameters tab and set  $\alpha_{\text{self}} = 1.79 \text{ Gy}^{-1}$ ,  $\beta_{\text{self}} = 0 \text{ Gy}^{-2}$ ,  $\alpha_{\text{cross}} = 1.79 \text{ Gy}^{-1}$ ,  $\beta_{\text{cross}} = 0 \text{ Gy}^{-2}$ . Click the Multicellular Geometry tab and then click the 3-D colony tab. From the drop-down list of Shapes, select Sphere. Enter a radius of 43  $\mu\text{m}$ . Select Labeling Method to be Uniform Distribution. Enter the Maximum mean Activity per Cell = 0.034 Bq. Enter the Time integrated activity coefficient = 6.1 h. Enter Percentage of cells that are Labeled = 100%. Click Compute.



- c. Click the Output tab and scroll down to the bottom of the data in the left box. Note that the mean absorbed dose to the cells is 138 Gy when the mean activity per cell is 0.034 Bq. This is commensurate with the values of 125-245 Gy reported in Ref. (5).

| Distance<br>µm | S(C<-C)<br>Gy/Bq-s | S(C<-CS)<br>Gy/Bq-s | S(N<-N)<br>Gy/Bq-s | S(N<-Cy)<br>Gy/Bq-s | S(N<-CS)<br>Gy/Bq-s | S(Cy<-N)<br>Gy/Bq-s | S(Cy<-CS)<br>Gy/Bq-s | S(Cy<-Cy)<br>Gy/Bq-s |
|----------------|--------------------|---------------------|--------------------|---------------------|---------------------|---------------------|----------------------|----------------------|
| 28             | 1.95E-03           | 1.99E-03            | 1.91E-03           | 1.94E-03            | 1.96E-03            | 1.94E-03            | 2.00E-03             | 1.98E-03             |
| 29             | 1.79E-03           | 1.81E-03            | 1.75E-03           | 1.78E-03            | 1.79E-03            | 1.78E-03            | 1.83E-03             | 1.81E-03             |
| 30             | 1.64E-03           | 1.66E-03            | 1.61E-03           | 1.63E-03            | 1.65E-03            | 1.63E-03            | 1.67E-03             | 1.66E-03             |
| 31             | 1.51E-03           | 1.53E-03            | 1.48E-03           | 1.51E-03            | 1.52E-03            | 1.51E-03            | 1.54E-03             | 1.53E-03             |
| 32             | 1.40E-03           | 1.41E-03            | 1.37E-03           | 1.39E-03            | 1.40E-03            | 1.39E-03            | 1.42E-03             | 1.41E-03             |
| 33             | 1.29E-03           | 1.31E-03            | 1.27E-03           | 1.29E-03            | 1.30E-03            | 1.29E-03            | 1.32E-03             | 1.31E-03             |
| 34             | 1.20E-03           | 1.21E-03            | 1.18E-03           | 1.20E-03            | 1.20E-03            | 1.20E-03            | 1.22E-03             | 1.21E-03             |
| 35             | 1.12E-03           | 1.13E-03            | 1.10E-03           | 1.11E-03            | 1.12E-03            | 1.11E-03            | 1.13E-03             | 1.13E-03             |
| 36             | 1.04E-03           | 1.05E-03            | 1.03E-03           | 1.04E-03            | 1.05E-03            | 1.04E-03            | 1.06E-03             | 1.05E-03             |
| 37             | 9.75E-04           | 9.82E-04            | 9.63E-04           | 9.73E-04            | 9.77E-04            | 9.73E-04            | 9.85E-04             | 9.81E-04             |
| 38             | 9.12E-04           | 9.17E-04            | 9.03E-04           | 9.11E-04            | 9.14E-04            | 9.11E-04            | 9.18E-04             | 9.16E-04             |
| 39             | 8.54E-04           | 8.58E-04            | 8.48E-04           | 8.54E-04            | 8.56E-04            | 8.54E-04            | 8.57E-04             | 8.56E-04             |
| 40             | 7.99E-04           | 7.99E-04            | 7.97E-04           | 8.00E-04            | 8.00E-04            | 8.00E-04            | 7.99E-04             | 7.99E-04             |
| 41             | 7.47E-04           | 7.45E-04            | 7.49E-04           | 7.48E-04            | 7.47E-04            | 7.48E-04            | 7.45E-04             | 7.45E-04             |
| 42             | 6.97E-04           | 6.95E-04            | 7.03E-04           | 6.98E-04            | 6.96E-04            | 6.98E-04            | 6.94E-04             | 6.94E-04             |
| 43             | 6.50E-04           | 6.46E-04            | 6.58E-04           | 6.50E-04            | 6.47E-04            | 6.50E-04            | 6.46E-04             | 6.47E-04             |

## References

1. Howell RW, Rao DV, Hou D-Y, Narra VR, Sastry KSR. The question of relative biological effectiveness and quality factor for Auger emitters incorporated into proliferating mammalian cells. *Radiat Res.* 1991;128:282-292.
2. Bolch WE, Eckerman KF, Sgouros G, Thomas SR. MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature. *J Nucl Med.* 2009;50:477-484.
3. Neti PVS, Howell RW. Biological response to nonuniform distributions of  $^{210}\text{Po}$  in multicellular clusters. *Radiat Res.* 2007;168:332-340.
4. Howell RW, Rajon D, Bolch WE. Monte Carlo simulation of irradiation and killing in three-dimensional cell populations with lognormal cellular uptake of radioactivity. *Int J Radiat Biol.* 2012;88:115-122.
5. Chouin N, Lindegren S, Frost SH, et al. Ex vivo activity quantification in micrometastases at the cellular scale using the alpha-camera technique. *J Nucl Med.* 2013;54:1347-1353.