Nanoparticle Toxicity

Mathematical Modelling

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Outline

Last time

1. Biology
2. Experiments
3. Experimental Results
4. Some Modelling Assumptions
5. Modelling Uptake

Today:

1. Compartment Model
2. Parameter Estimation
3. Modelling Results
4. Future Work

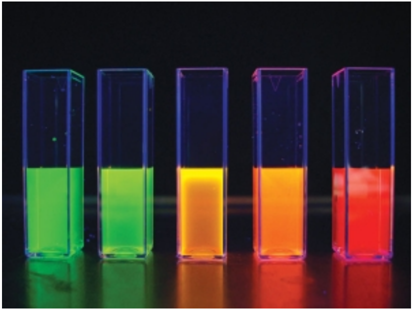


Figure: Various sizes of QDs

Gun'ko group, TCD

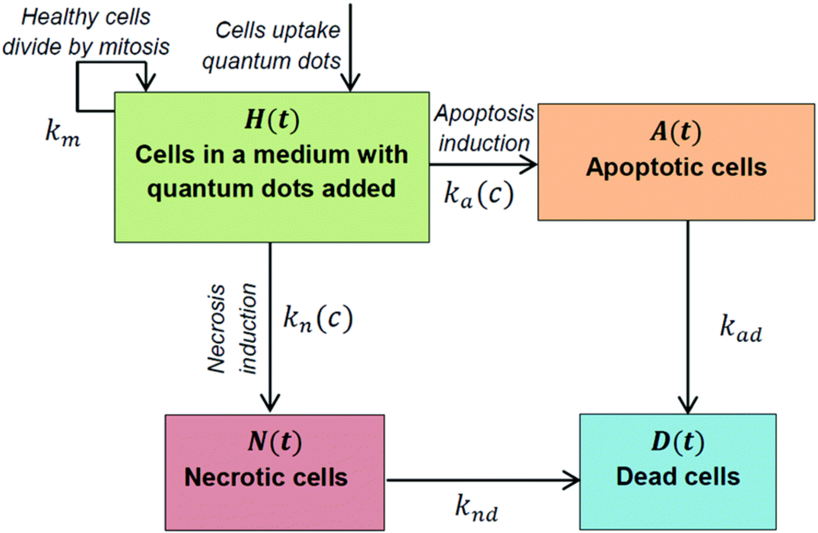
Some Modelling Assumptions

- Four states: healthy, apoptotic, necrotic, dead.
- Healthy cells can enter apoptosis or necrosis.
- Cells in apoptosis or necrosis can die.
- No reversibility.
- Rate at which cells leave healthy state depends on QD concentration.

Uptake model: saturation concentration c_s and current intracellular concentration $c(t)$ with

$$c(t) = c_s(1 - e^{-k_c t}). \tag{1}$$

Model Schematic



Model Equations

Assuming $k_a(c)$ and $k_n(c)$ are linear in c we have

$$\frac{dA(t)}{dt} = k_{a1} c_s (1 - e^{-k_c t}) H(t) - k_{ad} A(t), \quad (2)$$

$$\frac{dN(t)}{dt} = k_{n1} c_s (1 - e^{-k_c t}) H(t) - k_{nd} N(t), \quad (3)$$

$$\frac{dH(t)}{dt} = (k_m - k_{a1} c_s (1 - e^{-k_c t}) - k_{n1} c_s (1 - e^{-k_c t})) H(t), \quad (4)$$

$$\frac{dD(t)}{dt} = k_{ad} A(t) + k_{nd} N(t). \quad (5)$$

Here k_m is the rate of cell division. Initial conditions:

$$H(t=0) = H_0, A(t=0) = N(t=0) = D(t=0) = 0.$$

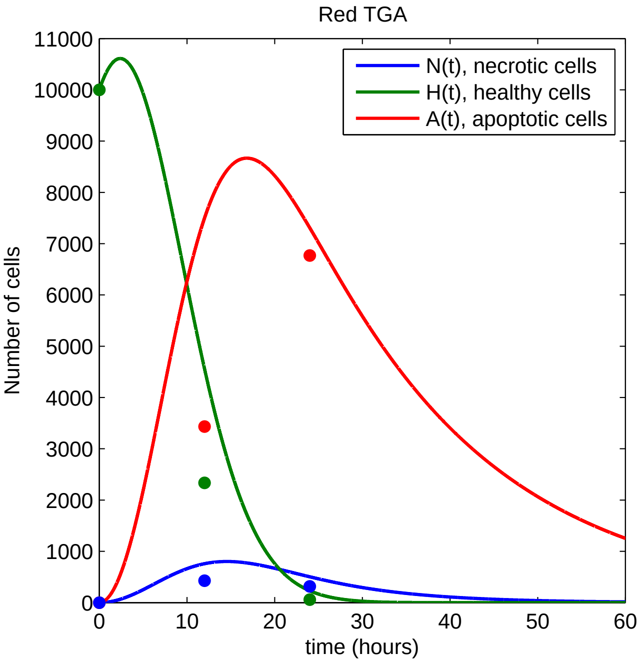
Estimation

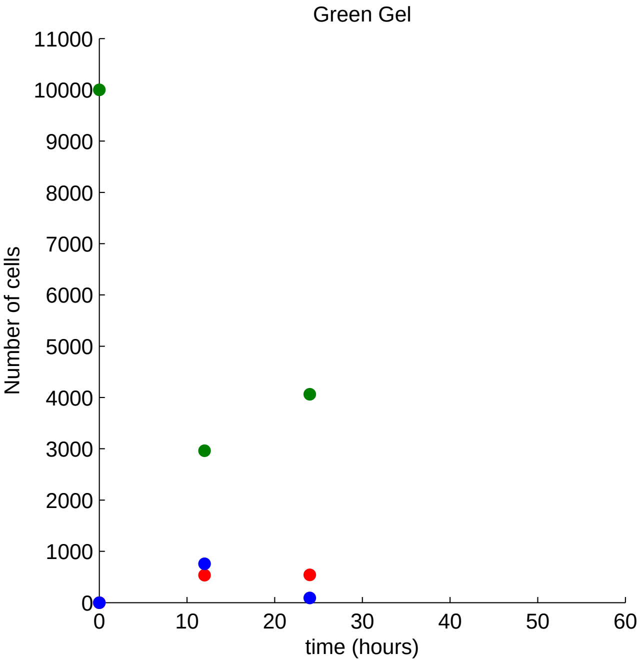
For each type of QDs, need to estimate k_{a1}, k_{n1}, c_s, k_c, k_{ad}, k_{nd}, k_m.

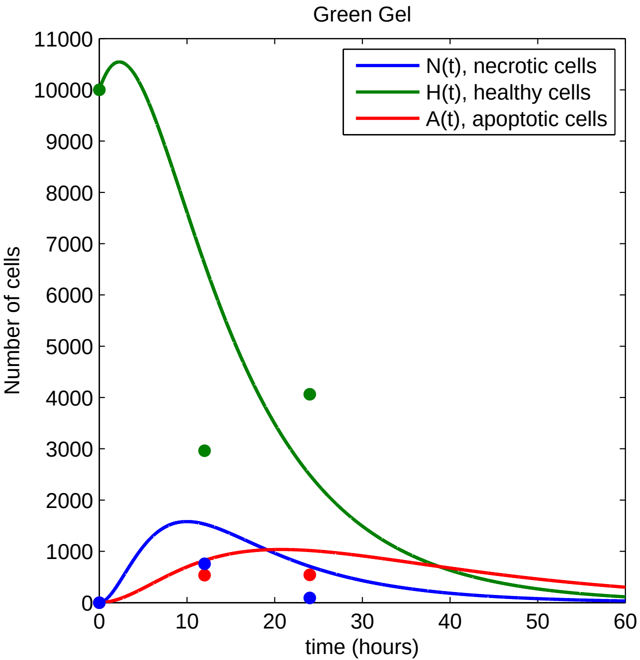
- Apoptosis takes from 6-24 hours $\implies k_{ad} \approx 0.05hr^{-1}$.
- Doubling time for RAW 264.7 is $\sim$ 12 hours

$$\implies k_m \approx \frac{\ln 2}{12} \approx 0.05hr^{-1}$$

- Treat $k_{a1}c_s$, $k_{n1}c_s$ as single parameters (only appear as products).
- Remains to estimate $k_{a1}c_s$, $k_{n1}c_s$, k_c, k_{nd} for each type.


Red TGA
N(t), necrotic cells
H(t), healthy cells
A(t), apoptotic cells
Number of cells
time (hours)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
0
10
20
30
40
50
60


Green Gel
Number of cells
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0
10
20
30
40
50
60
time (hours)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40
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60

Future Work

- Need further information on uptake;
  - timescale and saturation concentration not measured;
  - differ for each type;
  - Insufficient number of time points;
- Linear assumption of transition rates probably too simple
- Stage of the cell cycle may have an effect on uptake

References

Olga Gladkovskaya, Paul Greaney, Yurii K. Gun'ko, Gerard M. O'Connor, Martin Meere and Yury Rochev.
An experimental and theoretical assessment of quantum dot cytotoxicity.
Toxicology Research, 2015, **4**, 1409–1415