# The cycle begins: A multistage mathematical model of nanoparticle-cell interactions

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## Introduction

In recent years, delivery of small drugs to specific cells has been enhanced by the utilisation of nano-engineered particles. Measuring association between nanoparticles and cells has been crippled by the core use of qualitative experimental methods, such as fluorescent-based approaches.

To combat the lack of a quantitative method of analysis, Faria et al., (2019) developed a promising partial differential equation (PDE) based approach to analyse nanoparticle-cell interactions. Results depicted a cell carrying capacity (CCC) model, where the maximum number of particles able to associate with a cell is considered, as being the simplest and best performing method when compared to experimental results.

From the strong foundation provided by Faria et al., (2019), we aimed to incorporate multiple stages of the cell cycle to the base model. Cells continuously replicate and differences in association between stages is necessary for efficacious delivery of drugs into cells via nanoparticles.

## Cell Cycle Model

Faria et al., (2019) discerned the PDE model as being closely represented by an advection-diffusion PDE. In this case, particles in media are transported due to diffusive (D; units $m^2 s^{-1}$) and sedimentary (s; units $ms^{-1}$) forces before encountering adherent cells attached to a dish base. The term accounting for the diffusion coefficient and sedimentary vector, as a function of the particle concentration ($mol\ m^{-3}$) in solution ($u$), was determined as $f_{fluid}(u) = -D\nabla u + su$.

At the air-liquid media boundary, no particles can leave the solution inducing a zero-flux boundary condition. At the liquid media-cell boundary, the CCC model represents kinetics of nanoparticle-cell association which can be modelled by $f_{cell}(u) = SC \cdot r \cdot \frac{P_{cap} - P_{assoc}(t)}{P_{cap}} \cdot u$, where $SC$ is the surface coverage of the cells, $r$ ($ms^{-1}$) is the rate of nanoparticle-cell association, $P_{cap}$ ($mol\ m^{-3}$) is the maximum capacity of particles per cell, and $P_{assoc}(t)$ ($mol\ m^{-3}$) is the current number of associated particles.

This produces the following base PDE model, a corner stone of the two-stage cell cycle model:

$$\begin{aligned} \frac{\partial u}{\partial t} &= -\nabla \cdot f_{\text{fluid}}(u) \\ f_{\text{fluid}}(u) &= 0 \text{ on air-liquid boundary} \\ f_{\text{fluid}}(u) &= f_{\text{cell}}(u) \text{ on liquid-cell boundary} \end{aligned} \tag{1}$$

Utilising the same PDE and two boundary conditions, the cell cycle model is split into two stages. As the cycle is conducted in four phases ($G_1$, S, $G_2$, Mitosis) before division (cytokinesis), an important first stage is the initial growth phase ($G_1$) which constitutes $30-40\%$ of the cell cycle. The second stage then reunited the remainder of the phases (S, $G_2$, M) with cells splitting into two equally sized daughter cells at the end of the second stage. We need to keep track of the number of cells and the particles going into each cell type at every time step when solving the PDE. These values can be tracked by four new ODEs modelling the system (with $f_{cell}$ now considering these new tracking measurements):

$$\frac{dG}{dt} = 2T_{MG} \cdot M \cdot (1 - M - G) - T_{GM} \cdot G \tag{2}$$

$$\frac{dM}{dt} = T_{GM} \cdot G - T_{MG} \cdot M \cdot (1 - M - G) \tag{3}$$

$$\begin{aligned} SC(t) &= G(t) + M(t) \\ P_{cap}(t) &= P_{cap}(0) \cdot SC(t) \cdot \frac{\text{Area of dish base}}{\text{Surface area of one cell}} \\ r(t) &= r_G \cdot \frac{G(t)}{SC(t)} + r_M \cdot \frac{M(t)}{SC(t)} \\ \frac{dP_G}{dt} &= -T_{GM} \cdot P_G + T_{MG} \cdot P_M \cdot (1 - M - G) \\ &\quad + \frac{du_{lost}}{dt} \cdot \frac{r_G \cdot G(t)}{r_G \cdot G(t) + r_M \cdot M(t)} \left(1 - \frac{P_G}{P_{cap}(0) \cdot G \cdot \frac{\text{Area of dish base}}{\text{Surface area of one cell}}}\right) \end{aligned} \tag{4}$$

$$\begin{aligned} \frac{dP_M}{dt} &= T_{GM} \cdot P_G - T_{MG} \cdot P_M \cdot (1 - M - G) \\ &\quad + \frac{du_{lost}}{dt} \cdot \frac{r_M \cdot M(t)}{r_G \cdot G(t) + r_M \cdot M(t)} \left(1 - \frac{P_M}{P_{cap}(0) \cdot M \cdot \frac{\text{Area of dish base}}{\text{Surface area of one cell}}}\right) \end{aligned} \tag{5}$$

where $G(t)$, $M(t)$ are the proportion of current cells (with respect to surface coverage) in G or M stage, respectively, $T_{GM}$, $T_{MG}$ are rates of transition from G to M or M to G stages, respectively, $r_G$, $r_M$ are the rates of nanoparticle-cell association in G and M stages, respectively, $P_G(t)$, $P_M(t)$ are the current number of associated particles in G and M stages, respectively, and $u_{lost}$ is the number of particles going into the cell layer.

## Results

Using a backward space and time discretisation in (1) and a forward time discretisation in (2)-(5), the model can be solved over 24 hours with 10 second time steps and 1000 grid points. Utilising rates of transition in going from different stages of the cell cycle (Johnston et al., 2020) and 214 nm nanoparticles interacting with HeLa cells (Faria et al., 2019), changes to parameters allow investigation to their effects on nanoparticle-cell interaction:

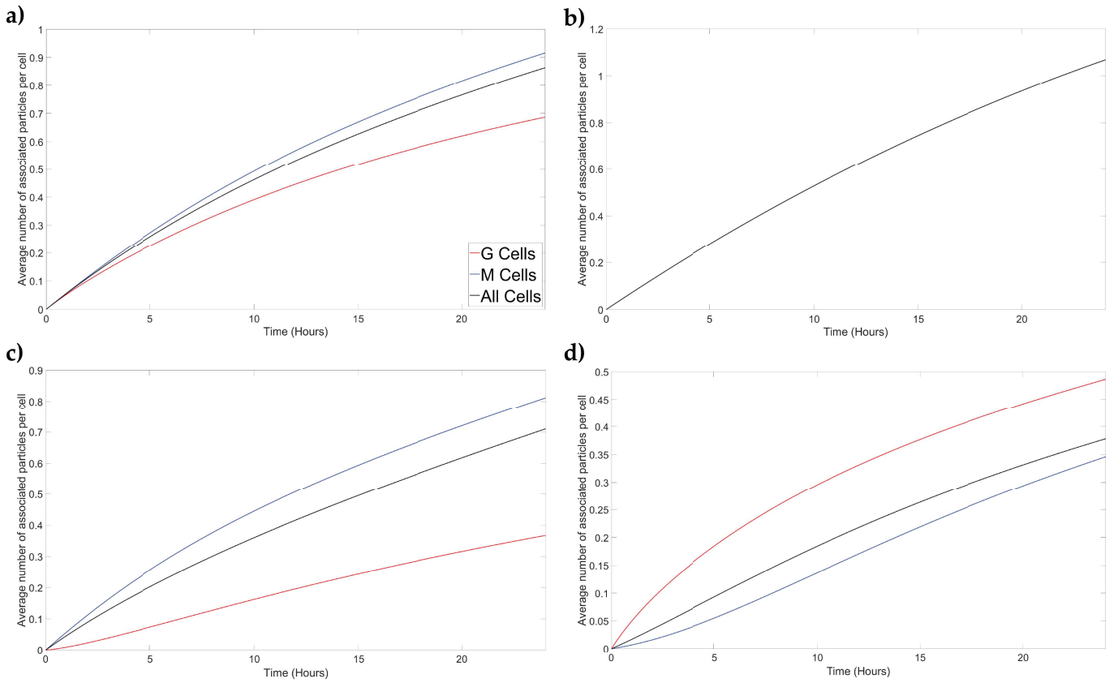


Fig. 1: Nanoparticle-cell interactions during a two-stage cell cycle ($20\%$ G cells, $80\%$ M cells). **(a)** G and M cells with identical particle association rates ($r_G = r_M = 10^{-9}$). **(b)** No transition between cell types ($T_{GM} = T_{MG} = 0$). **(c)** G cell rate of association reduced by a factor of 10 ($r_G = 10^{-10}$, $r_M = 10^{-9}$). **(d)** M cell rate of association reduced by a factor of 10 ($r_G = 10^{-9}$, $r_M = 10^{-10}$).

From Figure 1a, the average particles per cell increased but never reached the maximal capacity of 2 particles per cell. As M cells had a longer phase before transitioning to G cells, the average uptake of particles is much larger than the population of G cells. Setting cell transition rates to $0$ allowed for the curve defining the average uptake to follow that produced by Faria et al., (2019). As this indicated no cells transitioned from one stage to another, acting as a negative control, Figure 1b highlighted the model supported our results. Figure 1c, d indicate precisely that by lowering the respective uptake rates by a factor of $10$ for either population results in that population having a lower average uptake of nanoparticles.

## Conclusions

Retrospectively, the new two stage model for nanoparticle-cell interactions allows for new parameters to be investigated, such as cell transition rates, and their effects on nanoparticle uptake. Additional stages can be added to this model to allow for more complex variations. To verify the results, experimental quantities will need to be collected to confirm the accuracy of the model and whether the model needs to be altered.

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## References

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