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A Mathematical Model of Cyclin B1 Dynamics at the Single Cell Level in Osteosarcoma Cells

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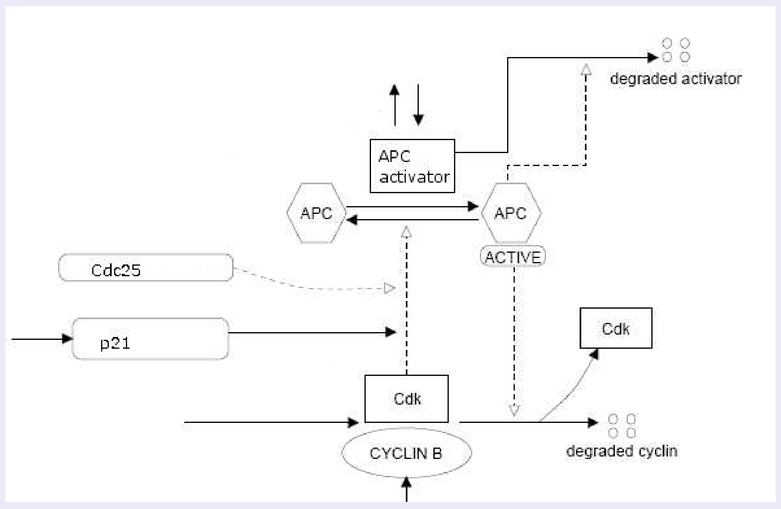
Summary

- Cyclin B1 tracking provides information on cell cycle progression and cell-cycle regulator dynamics
- We have developed a mathematical model which describes the continuous tracking of cyclin B1 through the cell cycle at the single cell level, including interactions with the cyclin B1 inhibitor, p_{21}
- The cell line used is a cancer cell line, human osteosarcoma (U-2 OS)
- A structural identifiability analysis was performed on the cell cycle model to ascertain the identifiability or otherwise of the (unknown) parameters within the model
- If all variables are observed (at least) four parameters were globally identifiable
- No parameters were globally identifiable (before running into computational problems) if Cyclin B is the only variable observed
- Assuming some of the parameters values are known, the two parameters used to fit the model to the data are globaly identifiable

The model

Schematic Diagram of system (1)



$$\frac{dy}{dt} = a_1 - (a_2 + a_3x + a_5A)y + C_2p_{21}, \quad (1a)$$

$$\frac{dx}{dt} = \frac{((k_1 + k_2A)(1 - x))}{(j_3 + 1 - x)} - \frac{(b_4mxy)}{(j_4 + x)} \quad (1b)$$

$$\frac{dm}{dt} = gm(1 - \frac{m}{m_s}) \quad (1c)$$

$$\frac{dA}{dt} = e_1A - e_2x \quad (1d)$$

$$\frac{dZ}{dt} = \frac{v_sy^4Z}{k_3^4 + y^4} - d_1Z \quad (1e)$$

$$\frac{dp_{21}}{dt} = -\frac{a_4y^4p_{21}}{c_3^4 + y^4} + c_4p_{21} \quad (1f)$$

Term $-c_2x$ in equation (1d) is a **negative feedback** of x on the production of A since an increase in x decreases the production of A. The larger the size of x, the smaller is the A production. **A is an activator of x** if $\frac{\partial f_1}{\partial A} > 0$. In our case $\frac{\partial f_1}{\partial A} = \frac{k_2(1-x)}{j_3+1-x}$ which is positive for our chosen parameter values.

Identifiability Analysis

- A key part of the analysis of the model involves comparing the model to the experimental data, which in turn involves parameter estimation
- To check whether the model parameters are uniquely determined by a given output, the Taylor series approach was used to explore the structural identifiability analysis of the model, this method allows application to high order non-linear system

Methodology

- We have developed a mathematical model of cyclin B1 progression through the cell cycle. We have used data arising from individual human osteosarcoma U-2 OS cells to validate the model.
- We solve system (1) numerically using the commercial simulation software package FACSIMILE (MCPA Software, UK), which uses a robust (implicit prediction-correction) numerical integrator, we use initial conditions $x(0) = 0.05; y(0) = 1.05; m(0) = 5; A(0) = 0.9; p(0) = 0.001; z(0) = 1.3$.
- We analyze the effects of varying the chosen parameter values to explore how they affect the cyclin B profile.
- We were unable to show that the model is identifiable even if we assume all variables are observed. We then proceed to assume that some of the parameters were known and we performed the analysis for fewer parameters.

Credits and Acknowledgments

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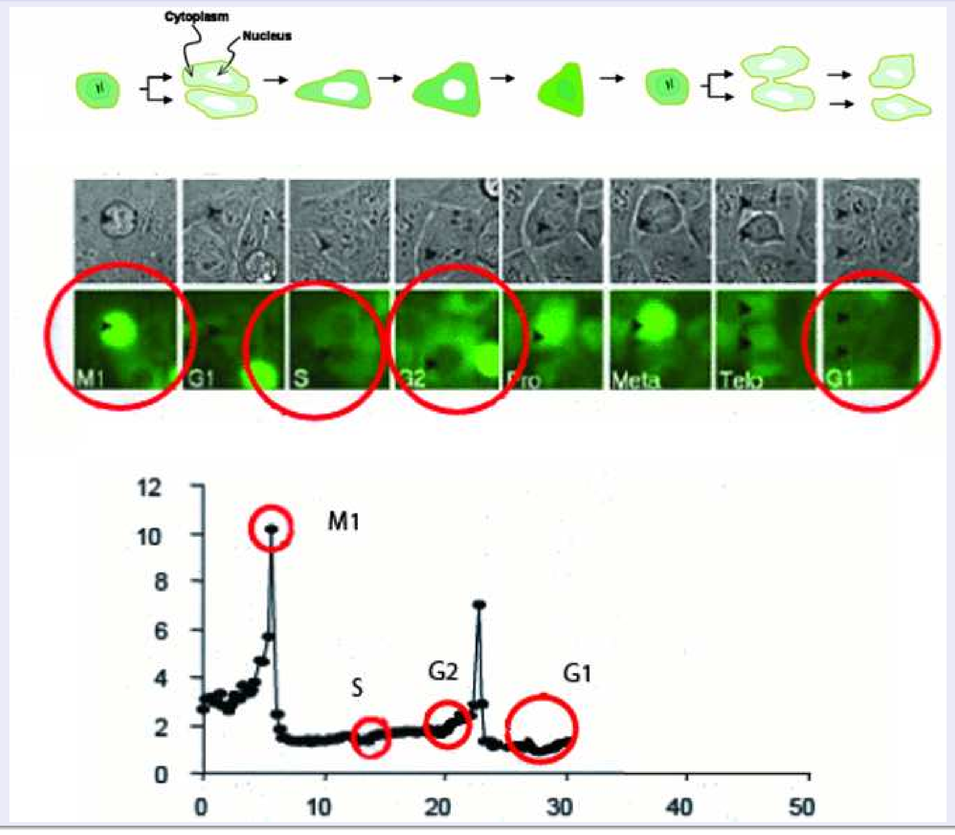
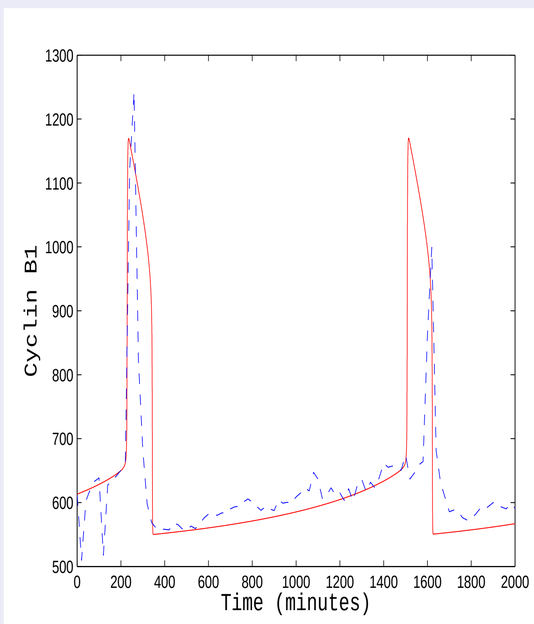
Continuous cell cycle tracking

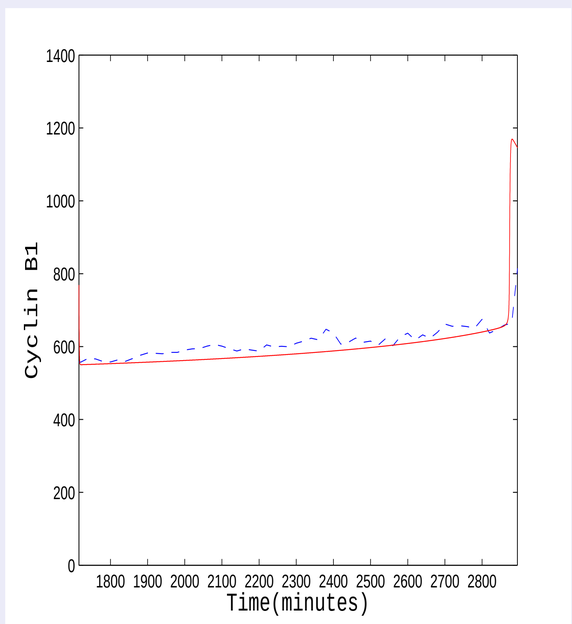


Comparison to Experimental (fluorescence) Data

Two mitotic events



One mitotic event



Simulated output from model (1) with parameters values $k_1' = 0.04$, $k_2' = 0.041$, $k_3' = 1$, $k_4' = 1$, $k_5' = 0.00015821$, $k_1'' = 1$, $k_2'' = 12$, $k_3'' = 0.04$, $k_4'' = 35$, $k_5'' = 0.04$, $g = 0.01$, $m_s = 10$, $a_1 = 0.0013$, $a_2 = 0.001$, $z_1 = 0.0016$, $z_2 = 0.0013$, $z_3 = 0.0013$, $p_1 = 0.0000008$, $p_2 = 0.0013$, $p_3 = 0.0001443$, (parameter fitting was performed on a_2 and k_5'), plotted (solid) against the experimental data (dotted).

Conclusions and Results

- The model reproduces several qualitative features, such how initial cyclin B concentration affect the time of first mitosis. We were able to detect which parameters have the greatest effect on the cyclin B profile.
- The model fits well to experimental data.
- Our model is an extended version of Novak and Tyson transition state cell cycle model and has been linked with a model accounting for the inhibition dynamics of p_{21} on cyclin B1.
- The model offers the possibility to infer information from parts of the system that are not directly measured.
- The model has also generated predictions that may be testable experimentally. Through the study of the sensitivity of the parameters we have been able to identify which (and how) parameters may affect important features of the cell cycle, like time between mitotic events, time of first mitotic event, number of mitotic events and cyclin levels.
- From the identifiability analysis was found that if only the Cyclin B measurement is available two parameters can be identified. A similar test on the two main equations of Tyson and Novak (for Cyclin and Cdh/APC) model showed that all parameters cannot be identified even if all variables are being measured. It is necessary to assume that some of the parameters are known.

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