Modeling Cell Division

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Abstract

When modeling cell division we began with six differential equations. Using various assumptions and reassigning variables we were able to get the system down to two ordinary differential equations. By plotting phase portraits for new system we found three different states the model can represent. When MPF activity is high then we are in a stable steady state associated with metaphase arrest. With Low MPF activity we see a stable steady state associated with growth-controlled division. Lastly, there is a unstable steady state associated with premature rapid division of the cell.

Introduction

A maturation promoting factor controlling the major events of the cell cycle is formed by the proteins in cdc2 and cyclin (Tyson, 1991). Using John J. Tyson's study on "Modeling the cell division cycle: cdc and cyclin interactions"this study will rework his ideas and expand on the analysis of the effect of different parameter values on the stability of the model. The mitotic cycles in both embryonic and somatic cells are believed to be controlled by the activity of the maturation promoting factor, an enzyme called MPF (Tyson, 1991). MPF is a heterodimer, composed of cyclin and a protein kinase called cdc2. It is understood that this interaction between cyclin and cdc2 generates MPF activity (see *Figure 1*)(Tyson, 1991).

Active MPF is known to stimulate many of the processes that are necessary for nuclear and cell division (Moreno- Nurse, 1990; Lewis, 1990). During the transition from metaphase to anaphase, the MPF complex dissociates while the cyclin subunit quickly degrades (Draetta et al., 1989). The cycle then repeats itself by the cyclin subunits combining with cdc2 subunits again, forming an inactive MPF complex which is then activated by dephosphorylation at a certain tyrosine reside of the cdc2 subunit (Gould & Nurse, 1989). This is important because MPF dissociation and cyclin proteolysis are necessary for the completion of the mitotic cycle.

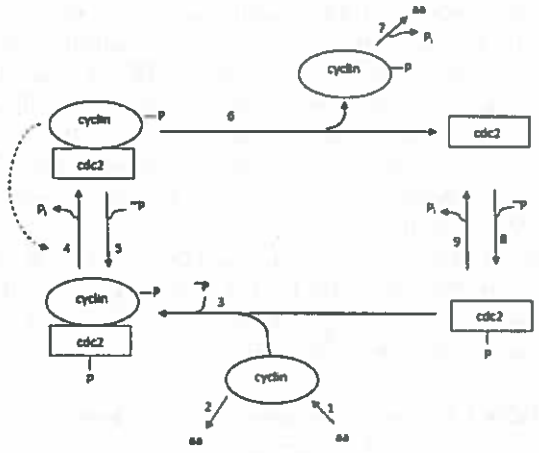

Figure 1: *Simplified view of cdc2-cyclin interactions Source: Tyson, 1991.*

Model

In order to determine if the simplified model (see *Figure 1*) is a reasonable approximation of the cell-cycle regulatory network, Tyson frames this model into precise mathematical equations. By investigating the properties of these equations, we can directly see the consequences of assumptions that were made to create the diagram in *Figure 1* (Tyson, 1991). The kinetic equations governing the cyclin-cdc2 cycle are shown below.

$$\frac{d[C2]}{dt} = k_6[M] - k_8[\sim P][C2] + k_4[CP] \quad (1)$$

$$\frac{d[CP]}{dt} = -k_3[CP][Y] + k_8[\sim P][C2] - k_4[CP] \quad (2)$$

$$\frac{d[pM]}{dt} = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M] \quad (3)$$

$$\frac{d[M]}{dt} = [pM]F([M]) - k_5[\sim P][M] - k_6[M] \quad (4)$$

$$\frac{d[Y]}{dt} = k_1[aa] - k_2[Y] - k_3[CP][Y] \quad (5)$$

$$\frac{d[YP]}{dt} = k_6[M] - k_7[YP] \quad (6)$$

These equations are dependent upon 10 parameters (see *Table 1*). Experimentally these values are unknown so here we are demonstrating that there exists numerical values for which the model shows dynamical behavior that is similar of that of cell-cycle control (Tyson 1991). In the above equations, concentrations [aa] and [~ P] are assumed to be constant thus there are six time-dependent variables. These time-dependent variables are as follows, [C2], the concentration of cdc2, [CP], the concentration of cdc2-P, [pM], concentration of $preMPF = P-cyclin-cdc2-P$, [M], concentration of active $MPF = P-cyclin-cdc2$, [Y], the concentration of cyclin and [YP] m the concentration of cyclin-P. The function F([M]) describes the autocatalytic feedback of active MPF on its own production (Tyson 1991).

Table 1. Parameters and values (*Source: Tyson 1991*)

Parameter	Value
$k_1[aa]/[CT]$	0.015 min^{-1}
k_2	0
$k_3[CT]$	200 min^{-1}
k_4	10-100 min^{-1}
$k_{4'}$	0.018 min^{-1}
$k_5[\sim P]$	0
k_6	0.1-10 min^{-1}
k_7	0.6 min^{-1}
$k_8[\sim P]$	>> k_9
k_9	>> k_6

Tyson focused on two parameters in his report: k_4 which is the rate constant describing the autocatalytic activation of MPF by dephosphorylation of the cdc2 subunit and k_6, which is the rate contact describing breakdown of the active cdc2-cyclin complex (Tyson 1991). These two parameters control if the system is stable or unstable as discussed later.

Using $u = [M]/[CT]$, $v = ([Y]+[pM]+[M])/[CT]$, $w = ([pM] + [M])/[CT]$ and $y = [YT]/[CT]$ we can reduce our set of kinetic equations to the follow four equations.

$$\frac{du}{dt} = k_4(w-u)f(u)k_6u \quad (7)$$

$$\frac{dv}{dt} = (k_1[aa]/[CT]) - k_2(v-w) - k_6u \quad (8)$$

$$\frac{dw}{dt} = k_3[CT](1-w)(v-w) - k_6u \quad (9)$$

$$\frac{dy}{dt} = (k_1[aa]/[CT]) - k_2(v-w) - k_7(y-v) \quad (10)$$

Where $f(u) = \alpha + u^2$ and $\alpha = k_{4'}/k_4$. Here, the first three equations can be solved independently of the fourth. Since w changes very rapidly compared to v, when $0 < v < 1$ then we can assume $w \approx v$. Therefore, the cdc2-cyclin model reduces to just two nonlinear ordinary differential equations.

$$\frac{du}{dt} = k_4(v-u)(\alpha + u^2) - k_6u \quad (11)$$

$$\frac{dv}{dt} = (k_1[aa]/[CT]) - k_6u \quad (12)$$

We now have two ordinary differential equations (see *Eq.11 and 12*) to represent our system and the rest of the analysis will be done using them.

Results and Analysis

The interactions of cdc2 and cyclin (*eq.11 and 12*) is evaluated to show the three types of modes this system operates in. Depending on the values of the parameters there is a stable steady state with high MPF activity, a stable steady state with low MPF activity and an unstable steady state. Below the global and local analysis is shown and discussed in relationship to our model. In each figure, the nullclines of our two equations are plotted and then arrows show the trajectory direction. Where the nullclines intersect is where a fixed point occurs. For the local analysis the Jacobian is evaluated at each fixed point. The Jacobian matrix in general is shown below.

$$J = \begin{bmatrix} 2k_4vu - k_4\alpha - 3k_4u^2 - k_6 & k_4\alpha + k_4u^2 \\ k_6 & 0 \end{bmatrix}$$

Steady State Behavior

High MPF activity

When $\frac{k_1[aa]}{k_6[CT]} > \sqrt{\frac{k_4}{k_4}}$ there is high MPF activity and the model shows a stable steady state. There is one fixed point and the global analysis (see *Figure 2*) shows a stable spiral. The local analysis gives complex eigenvalues with their real part negative. Thus,

locally the fixed point is also a stable spiral. Therefore, our control system of the cell acts in a stable state with everything spiraling towards the fixed point when there is high MPF activity. Thus when there is a lot of interaction between cyclin and cdc2 this state occurs.

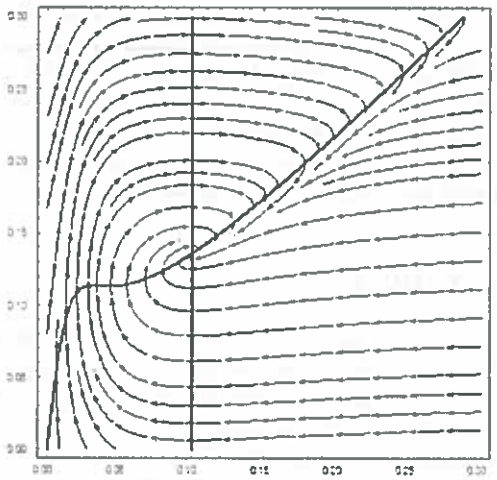

Figure 2: *Phase portrait for eqs. 11 and 12 with high MPF activity Source: Tyson, 1991.*

Low MPF activity

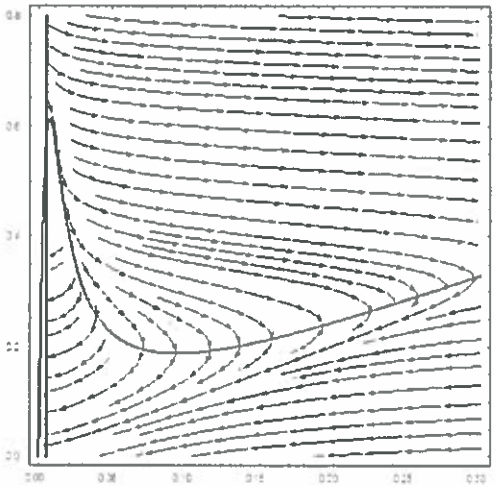

Figure 3: *Phase portrait for eqs. 11 and 12 with low MPF activity Source: Tyson, 1991.*

When $\frac{k_1[aa]}{k_6[CT]} < \sqrt{\frac{k_{4'}}{k_4}}$ there is low MPF activity but the model still shows a stable steady state. There is one fixed point and the global analysis shows there appears to be an invariant manifold (see *Figure 3*) that is causing the trajectories to eventually attract towards u,v=0. When zoomed in on the phase portrait you still can see the stable nature of the area near the fixed point. Locally, the fixed point is an attractor with both eigenvalues negative and real valued. Thus, this state occurs when there is a small interaction between cyclin and cdc2.

Unstable Steady State Behavior

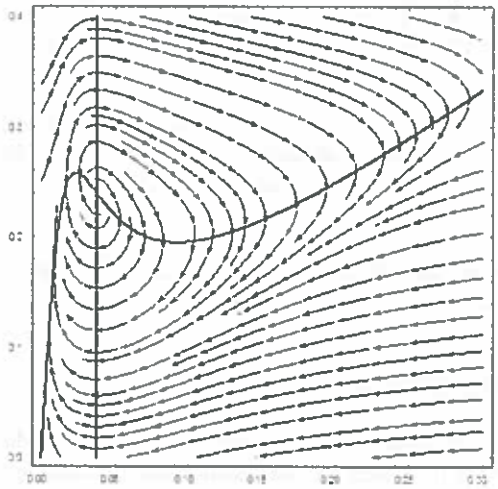

Figure 4: *Phase portrait for eqs. 11 and 12 for the unstable state with limit cycle oscillations. Source: Tyson, 1991.*

When $\sqrt{\frac{k_{4'}}{k_4}} < \frac{k_1[aa]}{k_6[CT]} < \sqrt{\frac{k_6}{k_4}}$ the control system runs in a unstable steady state. The global analysis (see *Figure 4*) shows a large stable spiral globally and what appears to be a small unstable spiral near the fixed point. Using local analysis, we obtained two complex eigenvalues with a positive real part which coincides with an unstable spiral. Thus, there is a limit cycle when the system operates under these conditions. The outline of the approximate location of the limit cycle is shown in blue (see *Figure 5*). We can conclude there is a limit cycle by applying the Poincare-Bendixon Theorem. We can construct a region in which all of the trajectories are contained within the region. Such a region is known as a trapping region. There is only the one fixed point and thus no others appear in our region and we have global flow spiraling in and local flow spiraling out

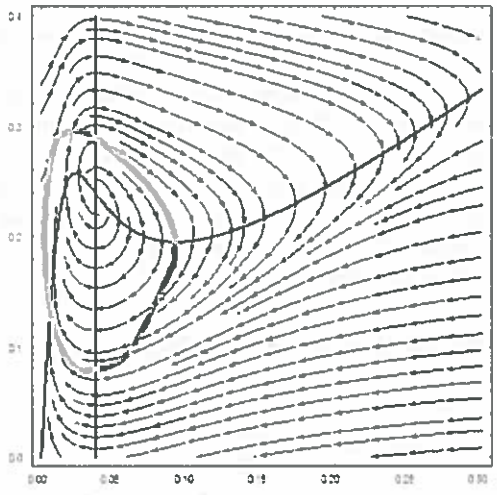

Figure 5: *Phase portrait for eqs. 11 and 12 for the unstable state highlighting the limit cycle in blue. Source: Tyson, 1991.*

thus by the Poincare-Bendixon Theorem there exists a limit cycle.

Discussion

As shown above, there are three states this model can operate in. Each of these states are associated with different cell function. The steady state with high maturation promoting factor activity, is associated with metaphase arrest in unfertilized eggs (Tyson 1991). This means the cell stops dividing during the stage of mitosis in which the eukaryotic cell has their chromosomes at their second-most condensed and coiled stage. Thus when there is high MPF activity and thus high cyclin and cdc2 interaction we see the cells undergo metaohase arrest.

The unstable steady state (spontaneous oscillator) is associated with rapid division within cycles in their early embryonic stage (Tyson 1991). This means that the division of the cell is occurring prematurely and at a very high rate.

Lastly, the stable steady sate with low MPF activity is associated with growth-controlled division cycles typical of non-embryonic cells (Tyson 1991). Here, the activity of MPF is low thus there is small interaction between cyclin and cdc2 leading to growth-controlled division.

Understanding the process of cell division and what drives it is very important because cell division is an essential stage in the life of all cells. If we are able to get accurate models of how cells divide in different situations then we can better understand and test treatment options as well as predict behaviors.

Conclusion

The analysis of models such as this one modeling cell division will play an increasingly important role in the understanding of cell-cycle control. Currently there is still a lot unknown about cell division and how to model its behavior but as our knowledge grows our models will become more accurate and have less assumptions associated with them.

References

Tyson, J J. 1991. "Modeling the Cell Division Cycle: cdc2 and Cyclin Interactions." *Proceedings of the National Academy of Sciences 88* (16): 732832. doi:10.10 73/pnas.88.16.7328.

Moreno, S. & Nurse, P. (1990) *Cell* 61, 549-551

Lewin, B. (1990) *Cell* 61, 742-752

Draette, G., Luca, F., Westendorf, J., Brizuela, L., Ruderman, J. & Beach, D. (1989) *Cell* 56, 829-838

Gould, K. L. & Nurse, P. (1989) *Nature (London)* 342,39-45