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Does Wee1 inhibit the entry to M phase?

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ABSTRACT

Active Wee1 is believed to have negative effect on the entry to M phase. It seems quite obvious since active Wee1 helps adding a phosphate to the tyrosine-15 (Tyr15) site of the active M phase promoting factor to make it inactive. But on the other hand, acitve Wee1 can also adds a phosphate to the non-phosphorylated M phase promoting factor (MPF), the product then has a great chance to become active too. In this way, Wee1 act positively on the entry to M phase. This paper addressed the question that whether Wee1 inhibits or promotes M phase through a mathematical point of view. Both assumptions, the mass action and the Michaelis-Menten, are discussed. Under the assumption of mass action Wee1 always inhibits the M phase, while under Michaelis-Menten, it depends on the certain condition of steady state concentrations of two different forms of MPF. Biological experiments suggest that the condition is hold so that Wee1 does inhibit M phase.

1 Introduction

Cell cycle consists of several phases, of which M phase exhibits the most dramatic changes. The driven factor of M phase is believed to be the active form of MPF, see [4]. MPF is a complex formed by cdc2 and cyclin B. There are two phosphorylation sites on MPF, Tyr15 and Thr161, which leads to four different forms of MPF, but MPF is active only when Thr161 site is phosphorylated, denoted as MPF-P.

Wee1 and cdc25 are the kinase and phosphatase for the phosphorylation at site Tyr15 respectively. Active Wee1 helps to add a phosphate to the Tyr15. In this way, Wee1 either makes MPF-P to be phosphorylated at both Tyr15 and Thr161 (denoted as P-MPF-P) or makes non-phosphorylated MPF (denoted as MPF) to be phosphorylated at the Tyr15 site, denoted as P-MPF. On the other hand, cdc25 removes a phosphate from the Tyr15. It activates P-MPF-P or makes MPF from P-MPF. This process can be better seen in Figure 1. Notice that the real system also has negative (respectively, positive) feedback from MPF-P to active Wee1 (respectively, active cdc25). The feedback will give rise to a very interesting bistablility phenomena, see [2]. For the purpose of this paper, we cut the feedback and focus on the open loop system.

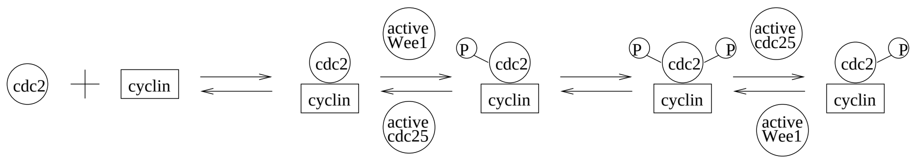

Figure 1: The conversions between different forms for MPF. The last complex is the active form of MPF.

Biological experiments proved that active Wee1 has negative effect on the entry to M phase, see [3] and [1]. But this is not obvious at all from Figure 1. The point of this paper is to contribute a better understanding of this fact in a mathematical way. The organization of the paper is as follows. Section 2 proved the negative effect of Wee1 under the assumption of mass action. Section 3 showed that under certain condition, the same conclusion still holds with the assumption of Michaelis-Menten. A counterexample is constructed where the condition is violated. Section 4 summarized the results and discussed possible directions to go beyond this problem.

2 Negative effect under the assumption of mass action

Under the assumption of mass action, we can actually prove the result for a larger class of chemical reactions. Consider the following chemical reactions of various forms of protein C:

$$B_0 + C_0 \rightleftharpoons C_1 \underset{V}{\overset{U}{\rightleftharpoons}} C_2 \cdots \underset{V}{\overset{U}{\rightleftharpoons}} C_n \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} C_{n+1} \cdots \underset{U}{\overset{V}{\rightleftharpoons}} C_{2n-1} \underset{U}{\overset{V}{\rightleftharpoons}} C_{2n}$$

The special case of $n = 2$,

$$B_0 + C_0 \rightleftharpoons C_1 \underset{V}{\overset{U}{\rightleftharpoons}} C_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C_3 \underset{U}{\overset{V}{\rightleftharpoons}} C_4,$$

corresponds to Figure 1 where cdc2, cyclin B, MPF, P-MPF, P-MPF-P, MPF-P, active Wee1 and active cdc25 are denoted as $B_0, C_0, C_1, C_2, C_3, C_4, U$ and V respectively.

Let's use the small letter for the concentration, and write down the differential equations:

$$\begin{aligned}
\dot{b}_0 &= -\sigma(b_0, c_0) + \gamma(c_1) \\
\dot{c}_0 &= -\sigma(b_0, c_0) + \gamma(c_1) \\
\dot{c}_1 &= \sigma(b_0, c_0) - \gamma(c_1) - \alpha_1(u)c_1 + \beta_2(v)c_2 \\
\dot{c}_2 &= \alpha_1(u)c_1 - \beta_2(v)c_2 - \alpha_2(u)c_2 + \beta_3(v)c_3 \\
\vdots &\;\vdots\; \vdots \\
\dot{c}_i &= \alpha_{i-1}(u)c_{i-1} - \beta_i(v)c_i - \alpha_i(u)c_i + \beta_{i+1}(v)c_{i+1} \\
\vdots &\;\vdots\; \vdots \\
\dot{c}_n &= \alpha_{n-1}(u)c_{n-1} - \beta_n(v)c_n - k_n c_n + k_{-n}c_{n+1} \\
\dot{c}_{n+1} &= k_n c_n - k_{-n}c_{n+1} + \alpha_{n-1}(u)c_{n+2} - \beta_n(v)c_{n+1} \\
\vdots &\;\vdots\; \vdots \\
\dot{c}_{2n-i} &= -\alpha_{i+1}(u)c_{2n-i} - \beta_{i+2}(v)c_{2n-i-1} + \alpha_i(u)c_{2n-i+1} - \beta_{i+1}(v)c_{2n-i} \\
\vdots &\;\vdots\; \vdots \\
\dot{c}_{2n-1} &= -\alpha_2(u)c_{2n-1} + \beta_3(v)c_{2n-2} + \alpha_1(u)c_{2n} - \beta_2(v)c_{2n-1} \\
\dot{c}_{2n} &= -\alpha_1(u)c_{2n} + \beta_2(v)c_{2n-1}.
\end{aligned}$$

We make the natural assumptions:

1. σ is a differentiable function $[0, \infty) \times [0, \infty) \to [0, \infty)$. Its partial derivatives are both positive, and $\sigma(0, c) = \sigma(b, 0) = 0$ for any $b, c \in [0, \infty)$.

2. γ is a differentiable function $[0, \infty) \to [0, \infty)$ with positive derivative and $\gamma(0) = 0$.

3. α_i, β_i are differentiable functions $[0, \infty) \to [0, \infty)$ with positive derivatives and $\alpha_i(0) > 0, \beta_i(0) > 0$ for each i. Notice that if U (respectively, V) does not play a role in the reaction of $C_i \to C_{i+1}$ and $C_{2n-i} \to C_{2n-i+1}$ for some $i < n$, the corresponding α_i (respectively, β_{i+1}) will just be a positive constant.

4. $c_0 + \sum_{i=1}^{2n} c_i = c_T, b_0 + \sum_{i=1}^{2n} c_i = b_T$. Let's denote X as the intersection of $c_0 + \sum_{i=1}^{2n} c_i = c_T, b_0 + \sum_{i=1}^{2n} c_i = b_T$ with the nonnegative orthant of $\mathbf{R}^{2n+2}$. Notice that X is invariant.

With the above assumptions, we have

Theorem 1 *For any constant $u, v \in [0, \infty)$, the above system has an unique steady state $s = (\bar{b}_0, \bar{c}_0, \cdots, \bar{c}_{2n})$ in X, so s as a function of u and v is well defined. The partial derivative of $\bar{c}_{2n}$ with respect to u (respectively, v) is negative (respectively, positive), i.e. $\bar{c}_{2n}$ is a strictly decreasing (respectively, increasing) function of u (respectively, v).*

Proof: Setting the right hand sides of the differential equations to zero, we get:

$$\gamma(\bar{c}_1) = \sigma(\bar{b}_0, \bar{c}_0) \tag{1}$$
$$\bar{c}_i = \frac{\beta_{i+1}(v)}{\alpha_i(u)}\bar{c}_{i+1} \tag{2}$$
$$\bar{c}_n = \frac{k_{-n}}{k_n}\bar{c}_{n+1} \tag{3}$$
$$\bar{c}_{2n-i} = \frac{\alpha_i(u)}{\beta_{i+1}(v)}\bar{c}_{2n-i+1}, \tag{4}$$

where $1 \le i \le n-1$. If there are two steady states, say $s_1 = (\bar{b}_0^1, \bar{c}_0^1, \cdots, \bar{c}_{2n}^1)$ and $s_2 = (\bar{b}_0^2, \bar{c}_0^2, \cdots, \bar{c}_{2n}^2)$, without loss of generality, we can assume $\bar{c}_{2n}^1 \ge \bar{c}_{2n}^2$. Then it is easy to see that $\bar{c}_i^1 \ge \bar{c}_i^2$ for $1 \le i \le 2n$. By assumption 1 and 4,

$$\gamma(\bar{c}_1^1) = \sigma(\bar{b}_0^1, \bar{c}_0^1) \le \sigma(\bar{b}_0^2, \bar{c}_0^2) = \gamma(\bar{c}_1^2).$$

The equality has to hold and therefore $s_1 = s_2$. Since the steady state is unique, s as a function of u and v is well defined. By assumptions 1,2 and 3, s is also differentiable with respect to u and v. Next, we will show that $\frac{\partial \bar{c}_{2n}}{\partial u} < 0$.

It follows from (2), (3) and (4) that

$$\sum_{i=1}^{2n} \bar{c}_i = \bar{c}_{2n}\left(1 + \frac{k_{-n}}{k_n}\right)\left(1 + \sum_{i=1}^{n-1}\prod_{j=1}^{i}\frac{\alpha_j(u)}{\beta_{j+1}(v)}\right).$$

It looks complicated, but we only need the property that $\sum_{i=1}^{2n} c_i$ is increasing in u, then the assumption 4 will give $\frac{\partial \bar{b}_0}{\partial u} < 0$ and $\frac{\partial \bar{c}_0}{\partial u} < 0$. Differentiating both sides of (2) with respect to u, we have

$$\frac{\partial \bar{c}_1}{\partial u} = \frac{\partial \sigma}{\partial \bar{b}_0}\frac{\partial \bar{b}_0}{\partial u} + \frac{\partial \sigma}{\partial \bar{c}_0}\frac{\partial \bar{c}_0}{\partial u} < 0.$$

Since $\bar{c}_1 = \frac{k_{-n}}{k_n}\bar{c}_{2n}$, $\frac{\partial \bar{c}_{2n}}{\partial u} < 0$ also. The proof for $\frac{\partial \bar{c}_{2n}}{\partial v} > 0$ follows the same way.

□

For our special case of $n = 2$, theorem 1 says that the concentration of MPF-P is a strictly decreasing function of the concentration of Wee1, that is, Wee1 inhibits MPF-P. But one thing about enzyme reactions is that they do not follow the law of mass action directly, the rate of reaction reaches a maximal velocity at high substrate concentrations. In the next section the same problem is considered when we introduce saturation.

3 Negative effect under the assumption of Michaelis-Menten

Unfortunately, the same conclusion does not always hold when the saturation appears. Here is an example:

$$\begin{aligned}
\dot{b}_0 &= -b_0c_0 + c_1 \\
\dot{c}_0 &= -b_0c_0 + c_1 \\
\dot{c}_1' &= b_0c_0 - c_1 - \frac{1}{2}(u+1)\frac{c_1}{1+c_1} + \frac{c_2}{1+c_2} \\
\dot{c}_2 &= \frac{1}{2}(u+1)\frac{c_1}{1+c_1} - \frac{c_2}{1+c_2} - c_2 + 4c_3 \\
\dot{c}_3 &= c_2 - 4c_3 - \frac{c_3}{1+c_3} + \frac{1}{2}(u+1)\frac{c_4}{1+c_4} \\
\dot{c}_4 &= \frac{c_3}{1+c_3} - \frac{1}{2}(u+1)\frac{c_4}{1+c_4}
\end{aligned}$$

with

$$c_0 + c_1 + c_2 + c_3 + c_4 = 10 = b_0 + c_1 + c_2 + c_3 + c_4. \tag{5}$$

The system satisfies all the assumptions in section 2, replacing the law of mass action by Michaelis-Menten. Solving the steady state, we get

$$\begin{aligned}
\bar{b}_0\bar{c}_0 &= \bar{c}_1 \\
\bar{c}_1 &= \frac{-4\bar{c}_4}{-\frac{3}{2}(u+1)\bar{c}_4 - 1 + 3\bar{c}_4} \\
\bar{c}_2 &= 4\bar{c}_3 \\
\bar{c}_3 &= \frac{-\frac{1}{2}(u+1)\bar{c}_4}{-1 - \bar{c}_4 + \frac{1}{2}(u+1)\bar{c}_4}.
\end{aligned}$$

At $u = 1$, it follows from (5) that $\bar{c}_4(1) = 1$. So

$$\frac{\partial(\bar{c}_1 + \bar{c}_2 + \bar{c}_3)}{\partial u}|_{u=1} = -1. \tag{6}$$

Differentiating both sides of $\bar{b}_0\bar{c}_0 = \bar{c}_1$ with respect to u and using (6), one can get $\frac{\partial \bar{c}_4}{\partial u}|_{u=1} > 0$, see Figure 2 for the simulation of this system.

This example tells us that we need more conditions for $\frac{\partial \bar{c}_4}{\partial u} < 0$ to hold when there is

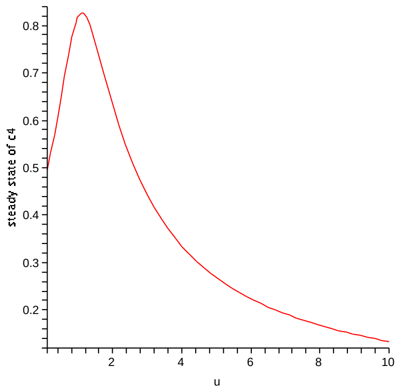

Figure 2: This is the simulation of the system above. At the beginning, the steady state of $\bar{c}_4$ is increasing with respect to u, which contradicts the result of section 2 that $\bar{c}_4$ is a strictly decreasing function of u.

saturation in the system. Consider

$$\begin{aligned}
\dot{b}_0 &= -\sigma(b_0, c_0) + \gamma(c_1) \\
\dot{c}_0 &= -\sigma(b_0, c_0) + \gamma(c_1) \\
\dot{c}_1 &= \sigma(b_0, c_0) - \gamma(c_1) - \alpha(u)\frac{c_1}{1+c_1} + \beta(v)\frac{c_2}{1+c_2} \\
\dot{c}_2 &= \alpha(u)\frac{c_1}{1+c_1} - \beta(v)\frac{c_2}{1+c_2} - \delta(c_2) + \eta(c_3) \\
\dot{c}_3 &= \delta(c_2) - \eta(c_3) - \beta(v)\frac{c_3}{1+c_3} + \alpha(u)\frac{c_4}{1+c_4} \\
\dot{c}_4 &= \beta(v)\frac{c_3}{1+c_3} - \alpha(u)\frac{c_4}{1+c_4},
\end{aligned}$$

with the assumptions:

1. σ is a differentiable function $[0,\infty) \times [0,\infty) \to [0,\infty) \times [0,\infty)$. Its partial derivatives are both positive, and $\sigma(0, c) = \sigma(b, 0) = 0$ for any $b, c \in [0,\infty)$.

2. γ, δ, η are differentiable functions $[0,\infty) \to [0,\infty)$ with positive derivatives and $\gamma(0) = \delta(0) = \eta(0) = 0$.

3. α, β are differentiable functions $[0,\infty) \to [0,\infty)$ with positive derivatives and $\alpha(0) > 0, \beta(0) > 0$.

4. $c_0 + \sum_{i=1}^4 c_i = c_T, b_0 + \sum_{i=1}^4 c_i = b_T$. Let's denote X as the intersection of $c_0 + \sum_{i=1}^4 c_i = c_T, b_0 + \sum_{i=1}^4 c_i = b_T$ with the nonnegative orthant of $\mathbf{R}^6$.

Theorem 2 *For any constant $u, v \in [0,\infty)$, the above system has an unique steady state $s = (\bar{b}_0, \bar{c}_0, \cdots, \bar{c}_4)$ in X, so s as a function of u and v is well defined. The partial derivative* *of $\bar{c}_4$ with respect to u (respectively, v) is negative (respectively, positive) if*

$$\eta' \bar{c}_3(\bar{c}_3 + 1) > \delta' \bar{c}_2(\bar{c}_2 + 1). \tag{7}$$

Proof: At the steady state we have

$$\begin{aligned} \gamma(\bar{c}_1) &= \sigma(\bar{b}_0, \bar{c}_0) \\ \bar{c}_1 &= \frac{\beta(v)\bar{c}_2}{\alpha(u) + \alpha(u)\bar{c}_2 - \beta(v)\bar{c}_2} \\ \delta(\bar{c}_2) &= \eta(\bar{c}_3) \end{aligned}$$

$$\bar{c}_3 = \frac{\alpha(u)\bar{c}_4}{\beta(v) + \beta(v)\bar{c}_4 - \alpha(u)\bar{c}_4}. \tag{8}$$

Let's think $\bar{c}_4$ as an independent variable for now, $\bar{c}_i$ ($i = 0, 1, 2, 3$) and b_0 are functions of u, v and $\bar{c}_4$. It is easy to see that $\frac{\partial \bar{c}_i}{\partial \bar{c}_4} > 0$ for $i = 0, 1, 2, 3$. Using the same argument in theorem 1, one can prove the uniqueness of s.

Next we claim that $\frac{\partial \bar{c}_1}{\partial u} > 0$, keeping in mind that we think $\bar{c}_1$ as a function of u, v and $\bar{c}_4$. By a straightforward calculation,

$$\frac{\partial \bar{c}_1}{\partial u} = \frac{\beta(v)}{(\alpha(u) + \bar{c}_2\alpha(u) - \bar{c}_2\beta(v))^2}(\alpha(u)\frac{\eta'}{\delta'}\frac{\partial \bar{c}_3}{\partial u} - \alpha'(u)\bar{c}_2 - \alpha'(u)\bar{c}_2^2).$$

It is positive if

$$\alpha(u)\frac{\eta'}{\delta'}\frac{\partial \bar{c}_3}{\partial u} > \alpha'(u)\bar{c}_2 + \alpha'(u)\bar{c}_2^2. \tag{9}$$

Because of (8),

$$\alpha(u)\frac{\partial \bar{c}_3}{\partial u} = \alpha'(u)(\bar{c}_3 + \bar{c}_3^2),$$

and (9) is equivalent to

$$\frac{\eta'}{\delta'}(\bar{c}_3 + \bar{c}_3^2) > \bar{c}_2 + c_2^2.$$

That is exactly (7).

From (9), we also get $\frac{\partial \bar{c}_3}{\partial u} > 0$, therefore $\frac{\partial \bar{c}_2}{\partial u} > 0$ also. Differentiating both sides of $\gamma(\bar{c}_1) = \sigma(\bar{b}_0, \bar{c}_0)$ with respect to u, we get

$$\gamma'(\frac{\partial \bar{c}_1}{\partial u} + \frac{\partial \bar{c}_1}{\partial \bar{c}_4}\frac{\partial \bar{c}_4}{\partial u}) + (\frac{\partial \sigma}{\partial \bar{b}_0} + \frac{\partial \sigma}{\partial \bar{c}_0})(\frac{\partial(\bar{c}_1 + \bar{c}_2 + \bar{c}_3)}{\partial u} + \frac{\partial(\bar{c}_1 + \bar{c}_2 + \bar{c}_3)}{\partial \bar{c}_4}\frac{\partial \bar{c}_4}{\partial u} + \frac{\partial \bar{c}_4}{\partial u}) = 0.$$

It can be written in the form $A + B\frac{\partial \bar{c}_4}{\partial u} = 0$, where

$$A = \gamma'\frac{\partial \bar{c}_1}{\partial u} + (\frac{\partial \sigma}{\partial \bar{b}_0} + \frac{\partial \sigma}{\partial \bar{c}_0})\frac{\partial(\bar{c}_1 + \bar{c}_2 + \bar{c}_3)}{\partial u},$$

$$B = \gamma'\frac{\partial \bar{c}_1}{\partial \bar{c}_4} + (\frac{\partial \sigma}{\partial \bar{b}_0} + \frac{\partial \sigma}{\partial \bar{c}_0})(\frac{\partial(\bar{c}_1 + \bar{c}_2 + \bar{c}_3)}{\partial \bar{c}_4} + 1).$$

Since $A > 0, B > 0, A + B\frac{\partial \bar{c}_4}{\partial u} = 0$, therefore $\frac{\partial \bar{c}_4}{\partial u} < 0$. The proof for $\frac{\partial \bar{c}_4}{\partial v} > 0$ follows the same way.

□

Let's try to understand biological meaning of condition (7). Since the reaction between C_2 and C_3 does not involve with U or V, we take $\delta(c_2) = k_2c_2$, $\eta(c_3) = k_3c_3$ for simplicity. Then (7) is equivalent to $\bar{c}_3 > \bar{c}_2$, which make sense intuitively. Because the reaction $C_1 \underset{V}{\overset{U}{\rightleftharpoons}} C_2$ is symmetric to $C_3 \underset{U}{\overset{V}{\rightleftharpoons}} C_4$, $\bar{c}_3 > \bar{c}_2$ means more C_4 than C_1, therefore the negative effect of U is stronger than the positive effect. But is this what really happens in the reality? The experiment carried out by Solomon, see [6], demonstrated clearly that the steady state concentration of P-MPF-P is significantly larger than P-MPF, i.e. $\bar{c}_3 > \bar{c}_2$. So the condition (7) is satisfied and Theorem 2 will guarantee that Wee1 does inhibit the entry to M phase.

Theorem 2 can be easily generalized to the reactions involving cooperativity:

$$
\begin{aligned}
\dot{b}_0 &= -\sigma(b_0, c_0) + \gamma(c_1) \\
\dot{c}_0 &= -\sigma(b_0, c_0) + \gamma(c_1) \\
\dot{c}_1 &= \sigma(b_0, c_0) - \gamma(c_1) - \alpha(u)\frac{c_1^{n_1}}{K_1^{n_1} + c_1^{n_1}} + \beta(v)\frac{c_2^{n_2}}{K_2^{n_2} + c_2^{n_2}} \\
\dot{c}_2 &= \alpha(u)\frac{c_1^{n_1}}{K_1^{n_1} + c_1^{n_1}} - \beta(v)\frac{c_2^{n_2}}{K_2^{n_2} + c_2^{n_2}} - \delta(c_2) + \eta(c_3) \\
\dot{c}_3 &= \delta(c_2) - \eta(c_3) - \beta(v)\frac{c_3^{n_3}}{K_3^{n_3} + c_3^{n_3}} + \alpha(u)\frac{c_4^{n_4}}{K_4^{n_4} + c_4^{n_4}} \\
\dot{c}_4 &= \beta(v)\frac{c_3^{n_3}}{K_3^{n_3} + c_3^{n_3}} - \alpha(u)\frac{c_4^{n_4}}{K_4^{n_4} + c_4^{n_4}}.
\end{aligned}
$$

Using a change of variable

$$
c_1^* = (c_1/K_1)^{n_1},\; c_2^* = (c_2/K_2)^{n_2},\; c_3^* = (c_3/K_3)^{n_3},\; c_4^* = (c_4/K_4)^{n_4},
$$

the equations become

$$
\begin{aligned}
b_0' &= -\sigma(b_0, c_0) + \gamma(K_1(c_1^*)^{1/n_1}) \\
c_0' &= -\sigma(b_0, c_0) + \gamma(K_1(c_1^*)^{1/n_1}) \\
(c_1^*)' &= \frac{n_1}{K_1}(c_1^*)^{(n_1-1)/n_1}(\sigma(b_0, c_0) - \gamma(K_1(c_1^*)^{1/n_1}) - \alpha(u)\frac{c_1^*}{1 + c_1^*} + \beta(v)\frac{c_2^*}{1 + c_2^*}) \\
(c_2^*)' &= \frac{n_2}{K_2}(c_2^*)^{(n_2-1)/n_1}(\alpha(u)\frac{c_1^*}{1 + c_1^*} - \beta(v)\frac{c_2^*}{1 + c_2^*} - \delta(K_2(c_2^*)^{1/n_2}) + \eta(K_3(c_3^*)^{1/n_3})) \\
(c_3^*)' &= \frac{n_3}{K_3}(c_3^*)^{(n_3-1)/n_3}(\delta(K_2(c_2^*)^{1/n_2}) + \eta(K_3(c_3^*)^{1/n_3}) - \beta(v)\frac{c_3^*}{1 + c_3^*} + \alpha(u)\frac{c_4^*}{1 + c_4^*}) \\
(c_4^*)' &= \frac{n_4}{K_4}(c_4^*)^{(n_4-1)/n_4}(\beta(v)\frac{c_3^*}{1 + c_3^*} - \alpha(u)\frac{c_4^*}{1 + c_4^*}).
\end{aligned}
$$

Since $\frac{\partial \bar{c}_4}{\partial u} > 0$ is equivalent to $\frac{\partial \bar{c}_4^*}{\partial u} > 0$, we have

Theorem 3 *For any constant $u, v \in [0, \infty)$, the above system has an unique steady state $s = (\bar{b}_0, \bar{c}_0, \cdots, \bar{c}_4)$ in X, so s as a function of u and v is well defined. The partial derivative of $\bar{c}_4$ with respect to u (respectively, v) is negative (respectively, positive) if*

$$\frac{\eta'}{n_3}\bar{c}_3((\frac{\bar{c}_3}{K_3})^{n_3} + 1) > \frac{\delta'}{n_2}\bar{c}_2((\frac{\bar{c}_2}{K_2})^{n_2} + 1). \tag{10}$$

As before, if we assume that $\delta(c_2) = k_2c_2, \eta(c_3) = k_3c_3$, (10) is equivalent to $((\frac{\bar{c}_3}{K_3})^{n_3}+1)/n_3 > ((\frac{\bar{c}_2}{K_2})^{n_2}+1)/n_2$. The biological mechanism for cdc25 to dephosphorylate P-MPF or P-MPF-P is similar, so we can take $n_2 = n_3$ and $K_2 = K_3$. Then (10) is equivalent to $\bar{c}_3 > \bar{c}_2$, which is consistent with the experiments by Solomon.

4 Conclusion and discussion

In this paper we discussed the question that whether active Wee1 has negative effect on the entry to M phase. Modeling the system directly by mass action, we get the conclusion that active Wee1 always inhibits the entry to M phase. While modeling the system through Michaelis-Menten, certain relation between the amount of P-MPF-P at the steady state and the amount of P-MPF at the steady state has to be satisfied to guarantee the same conclusion.

The result that active Wee1 has negative effect on MPF-P can be used to get further information about the dynamics of the system when we add the feedback from MPF-P to active Wee1 and active cdc25. If the closed-loop system is monotone, there are very powerful tools to analyze such system, see [5]. But of course the difficulty is how to prove the monotonicity.

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