



# On a family of models of cell division cycle

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## Abstract

The aim of this work is to generalize and study a model of cell division cycle proposed recently by Zheng et al. [Zheng Z, Zhou T, Zhang S. Dynamical behavior in the modeling of cell division cycle. *Chaos, Solitons & Fractals* 2000;11:2371–8]. Here we study the qualitative properties of a general family to which the above model belongs. The global asymptotic stability (GAS) of the unique equilibrium point  $E$  (idest of the arrest of cell cycling) is investigated and some conditions are given. Hopf’s bifurcation is showed to happen. In the second part of the work, the theorems given in the first part are used to analyze the GAS of  $E$  and improved conditions are given. Theorem on uniqueness of limit cycle in Lienard’s systems are used to show that, for some combination of parameters, the model has GAS limit cycles.

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## 1. Introduction and main results

The cell cycle is a fundamental phenomenon for the life. Furthermore, irregularities in the cell cycle are the one common factor in all the manifestation of human cancer [1]. Molecular biology investigations showed that the cycle is strictly linked with oscillations in the concentrations of a limited number of substances, such as cyclin, MPF and Cdc2. Mathematical modeling of the cell cycle in term of nonlinear models of the interaction between these substances started in early nineties [2,3]. A model in which the interaction between Cdc2, Cdc25, cyclin and MPF was proposed in [4]. It is a high dimensional system of nonlinear differential equations, but by way of biological simplifications and a linear transformation of variables, a dimensionally reduced model may be obtained, which depends only on two new state variables. Recently one of such bidimensional reduced models has been proposed and studied in the interesting paper [5], where some sufficient criteria for the existence of limit cycles and for the stability of the equilibrium point were given in the hypothesis that the contribution of one of the parameters can be neglected. In reality, in [5], an entire family of models has been defined, but the authors did not study it and they concentrated on a particular model. On the contrary, in the present work we will study the general family by showing that it is equivalent to a family of Generalized Lienard’s Systems. This is important in that some relevant properties such as the stability of the equilibrium point, the existence of limit cycles and, mainly, their uniqueness and global stability may be, at least in principle, easily studied. In the second part of this article, the model [5] is studied and we show that the our new criteria improve the ones given in

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[5]. Furthermore, it is shown that, for some values of the parameters, the limit cycle is (unique and) globally asymptotically stable. Numerical simulations complete the work to study the effect of periodic variation in parameters.

**2. A general family of models of cell cycle and its topological equivalence with the generalized Lienard’s systems**

Following [5], the biological mechanism underlying the cell cycle may be modeled by a couple of nonlinear differential equations (similar to the model [3]), which read (in adimensional form):

$$\begin{aligned} u'(t) &= \hat{\phi}K(u;p)(v - u) - (1 + K(u;p))u, \\ v'(t) &= c - K(u;p)v, \end{aligned} \tag{1}$$

where

- $u(t)$  is proportional to the concentration of Mitosis promoting factor;
- $v(t)$  is the sum of the concentrations of a set of other species, including the MPF, which implies, of course, the following constraint between the state variables:

$$v(t) > u(t)$$

(quite interestingly, Zhang et al. does not mention this biologically relevant fact);

- $K(u;p)$  is a continuous positive increasing function, which we will assume differentiable at least twice and  $p = (p_1, p_2, \dots)$  is a  $n$ -ple of positive parameters regulating the “shape” of  $K(u;p)$ . For sake of notational simplicity we will use also the shortened notation  $K(u)$ ;
- $c > 0, \hat{\phi} > 0$ .

In [5] it is studied a particular model, of great biological interest, derived from the family (1):

$$\begin{aligned} u'(t) &= \phi(a + u^2)(v - u) - (1 + b(a + u^2))u, \\ v'(t) &= c - b(a + u^2)v, \end{aligned} \tag{2}$$

where  $K(u) = b(a + u^2)$  (thus:  $p = (b, a)$ ,  $\phi = b\hat{\phi} > 0$ ,  $0 < a \ll 1$ ,  $b > 1$  and  $0 < c < 1$ ).

We will study in this section the family (1) and in the next section we will apply the results we are going to illustrate to (2).

The nullclines of (1) are:

$$v_1(u) = u \left( 1 + \frac{1}{\hat{\phi}} + \frac{1}{\hat{\phi}K(u)} \right), \quad v_2(u) = \frac{c}{K(u)} \tag{3}$$

and they are such that  $0 < v_2(u) \leq \frac{c}{K(0)}, (1 + \frac{1}{\hat{\phi}})u < v_1(u) \leq u \left( 1 + \frac{1}{\hat{\phi}} + \frac{1}{\hat{\phi}K(0)} \right)$ . Noting that  $(1 + \frac{1}{\hat{\phi}} + \frac{1}{\hat{\phi}K(0)})u \approx v_1'(0)u$  and that for  $u \gg 1$  it is  $v_1(u) \approx (1 + \frac{1}{\hat{\phi}})u$ , it not unrealistic to add this additional constraint: the equation  $v_1'(u) = 0$  has 0 or 2 solutions (idest or  $V_1(u)$  is increasing or it has a relative maximum and minimum).

A relatively small positively invariant set may be found:

$$\Gamma = \left\{ (u, v) \mid 0 < u < \frac{c}{K(0)} \left( 1 + \frac{1}{\hat{\phi}} \right)^{-1} \quad \text{and} \quad u \leq v \leq \frac{c}{K(0)} \right\}. \tag{4}$$

**Proposition 2.1.** *There is an unique equilibrium point  $E = (u_e, v_e)$  and it is such that  $\frac{\partial u_e}{\partial c} > 0$ .*

**Proof.** From  $v_1(u) = v_2(u)$  one obtains  $P(u) = 0$  where:

$$P(u) = (\hat{\phi} + 1)K(u)u + u - c\hat{\phi} \tag{5}$$

with  $P(0) < 0, \lim_{u \rightarrow +\infty} P(u) = +\infty$  and  $P'(u) > 0$ , thus there is an unique real solution  $u_e$ . Geometrically, it is straightforward to show that  $u_e$  is an increasing function of the parameter  $c$  and from the Dini’s theorem on implicit functions it is

$$\frac{\partial u_e}{\partial c} = \frac{\hat{\phi}}{1 + (\hat{\phi} + 1)(1 + u_e K'(u_e))} > 0. \quad \square \tag{6}$$

**Remark.** Remember that  $E$  is not fixed, but it is a function of the parameters  $p$  and  $c$ .

Noticing that  $u' = \hat{\phi}K(u)(v - v_1(u))$  and  $v' = K(u)(v_2(u) - v)$ , it is convenient to study the following system:

$$\begin{aligned} u'(t) &= v - v_1(u), \\ v'(t) &= v_2(u) - v, \end{aligned} \tag{7}$$

which is topologically equivalent [10] to (1) and which, after eliminating  $v$ , may be written as a generalized Lienard's equation:

$$u'' + f(u)u' + g(u)u = 0 \tag{8}$$

(idest  $u' = \eta - F(u)$ ,  $\eta' = -g(u)$ ) where the Lienard's functions are:

$$f(u) = 1 + \hat{\phi}v_1'(u), \tag{9}$$

$$g(u) = \hat{\phi}(v_1(u) - v_2(u)) = \hat{\phi} \frac{P(u)}{K(u)} \tag{10}$$

and

$$F(u) = \int_{u_e}^s (1 + \hat{\phi}v_1'(s)) ds = u - u_e + \hat{\phi}(v_1(u) - v_1(u_e)) \tag{11}$$

(of course  $F(u_e) = 0$ )

$$G(u) = \int_{u_e}^s g(s) ds. \tag{12}$$

Note that  $G(u)$  may be seen as a potential energy with of a single absolute minimum and it is  $\lim_{u \rightarrow +\infty} G(u) = +\infty$ . We are interested, of course, only to the zone corresponding to our invariant set.

It holds the following propositions:

**Proposition 2.2.** *If the parameters  $p$  and  $\hat{\phi}$  are such that  $f(u; p, \hat{\phi}) > 0$  then  $E$  is GAS.*

**Proof.** It is enough to take the “energy” as Liapunov–LaSalle's function:

$$L(u, u') = \frac{(u')^2}{2} + G(u) = \frac{(v - v_1(u))^2}{2} + G(u). \tag{13}$$

And apply the La Salle's theorem [9].  $\square$

It holds also this other proposition involving also the parameter  $c$ :

**Proposition 2.3.** *If the parameters  $c$  and  $p$  are such that  $f(u; \hat{\phi}, p) > 0$  in  $\Gamma$  then  $E$  is GAS.*

**Proof.** Apply the Dulac's theorem to (7) and the Poincaré–Bendixon's trichotomy.  $\square$

Linearizing near the equilibrium the characteristic equation is

$$\lambda^2 + (1 + \hat{\phi}v_1(u_e))\lambda + \frac{P'(u_e)}{K(u_e)} = 0. \tag{14}$$

Being  $\frac{P'(u_e)}{K(u_e)} > 0$  of course we obtain that if  $f(u_e) < 0$  then  $E$  is unstable. However, remembering that we supposed that  $v_1'(u)$  may have two solutions, the same must be also for  $f(u) = 0$  and let us call them  $u_M(p) < u_m(p)$ , we have that if it is

$$P(u_M) < 0 \quad \text{and} \quad P(u_m) > 0 \tag{15}$$

then it must be  $f(u_e) < 0$ . Defining the two values  $c_1 = Q(u_M)$  and  $c_2 = Q(u_m)$  and remembering that  $\Gamma$  is positively invariant one has that:

**Proposition 2.4.** *If  $c_1$  and  $c_2$  exist and*

$$c_1(p, \hat{\phi}) < c < c_2(p, \hat{\phi}) \tag{16}$$

*then  $E$  is unstable and there is at least a limit cycle.*

**Proposition 2.5.** *If  $c < c_1$  or  $c > c_2$  then  $E$  is LAS.*

For the global stability of  $E$ , idest of the cell cycle arrest, we may switch back to the original system (1) and state:

**Proposition 2.6.** *If the parameters  $c$  and  $p$  in  $\Gamma$  are such that  $f(u_e) < 0$  and such that in  $\Gamma$  the expression:*

$$N(u, v) = \hat{\phi}K'(u)(v - u) - (2 + \hat{\phi})K(u) - K'(u) - 1 \tag{17}$$

*has constant sign then  $E$  is GAS.*

**Proof.** The divergence of the vectorial field associated to 1 is equal to  $N(u, v)$ . If it has constant sign, the global asymptotic stability of  $E$  derives from the Poincaré–Bendixon’s trichotomy.  $\square$

Defining  $u_l \neq u_m | F(u_l) = F(u_m)$  and  $u_r \neq u_l | F(u_r) = F(u_M)$ , the analysis of the GAS of  $E$  may be further improved:

**Proposition 2.7.** *When  $c < c_1$  if for  $s \in (u_l, u_e)$  it is  $F(s) \neq F(Z_1(s))$  (where  $Z_1(s) = G^{-1}(G(s))$ ,  $s < u_e, Z_1(s) \neq s$ ) then  $E$  is GAS. When  $c > c_2$  if for  $s \in (u_e, u_r)$  it is  $F(s) \neq F(Z_2(s))$  (where  $Z_2(s) = G^{-1}(G(s))$ ,  $s > u_e, Z_2(s) \neq s$ ) then  $E$  is GAS.*

**Proof.** In such a case, it may be applied Lemma 9 of [7], in the form used in [8], and there are no closed orbits. Note that, being  $F(u)$   $N$ -shaped, for  $s < u_l$  ( $s > u_r$ ) it is automatically verified that  $F(s) \neq F(Z_1(s))$  ( $F(s) \neq F(Z_2(s))$ ): this means that if  $c < c_1$  and  $F(u_m) > 0$  ( $c > c_2$  and  $F(u_M) < 0$ ) then  $E$  is GAS. This is also why one has to test it only in  $(u_l, u_e)$ .  $\square$

Finally, we state the following conjecture based on geometrical arguments:

**Conjecture 2.8.** *For  $c < c_1$  ( $c > c_2$ )  $E$  is GAS.*

**Proof.** For  $c < c_1$  we saw that  $E$  is LAS. There might be some limit cycles. Moving  $c$  towards  $c_1$  a limit cycle might have the following behaviors:

- It might collapse with the frontier of  $\Gamma$ , which is impossible, since, for example, for whatever positive value of  $c$  the flux is direct towards the interior of  $\Gamma$ ;
- It might collapse with the equilibrium point, which is impossible since there is an unique supercritical Hopf’s bifurcation at  $c = c_1$ .

Therefore  $E$  should be stable.  $\square$

Coming back to the limit cycles it holds:

**Proposition 2.9.** *If  $v''(u_e) \neq 0$  then at  $c = c_1$  ( $c = c_2$ ) there is an Hopf’s bifurcation.*

**Proof.** Taking  $c$  as bifurcation parameter, the characteristic equation  $\lambda^2 + a_1\lambda + a_0$  is such that  $a_0 > 0$ ,  $a(c_1) = 0$ . When  $c = c_1 \Rightarrow u = u_M \Rightarrow a_1 = 0$  and

$$\frac{\partial a_1}{\partial c} = f'(u_e) \frac{\partial u_e}{\partial c} = \frac{\hat{\phi}}{1 + (\hat{\phi} + 1)(1 + u_e K'(u_e))} v''_1(u_e) \tag{18}$$

thus, if  $v''_1(u_e) \neq 0$  then there is an hopf’s bifurcation. Furthermore, since at  $c = c_1 \Rightarrow u_e = u_M$  the second derivative of  $v_1(u)$  when non zero is evidently negative, the bifurcation is supercritical. For  $c = c_2$  the proof is similar.  $\square$

The equivalence of (1) with the Lienard’s equation may allow to use some the theorem existing on the uniqueness of the limit cycle. The most widely known theorem in the field is the Zhang’s theorem [6], which, however requires the monotonicity of  $f(u)/g(u)$ , and some recent theorems [7] (or [8] where, however, a non essential condition on  $\eta$  was added, which does not appear in [7]).

**Remark.** *If the uniqueness and stability of the limit cycle is demonstrated, then, since the unique equilibrium point is unstable and since  $\Gamma$  is positively invariant, also the global asymptotic stability holds.*

### 3. Study of model (2)

In this section, we will apply the above propositions to (2). The functional form  $k(u) = b(a + u^2)$  makes the problem relatively simple in that all the above formulas may be analytically calculated. For example, the equilibrium equation

$P(u_e) = 0$  leads to the solution of a third degree algebraical equation, for which the well-known Cardano's formula is available. In particular it is

$$f(u) = \frac{1}{b} \frac{(2b + \phi)(u^2 + a)^2 - (u^2 + a) + 2a}{(u^2 + a)^2}, \tag{19}$$

$$G(u) = \frac{1}{2} \left( 1 + \frac{\phi}{b} \right) (u^2 - u_e^2) + \frac{1}{2b} \log \left( \frac{a + u^2}{a + u_e^2} \right) - \frac{c\phi}{b^2 \sqrt{a}} \left( \arctan \left( \frac{u}{\sqrt{a}} \right) - \arctan \left( \frac{u_e}{\sqrt{a}} \right) \right). \tag{20}$$

Thus, reading the numerator of  $f(u)$  as a parabolic function of  $(u^2 + a)$ , and calculating its discriminant, Proposition (2.2) becomes:

**Proposition 3.1.** *If*

$$8a(2b + \phi) > 1 \tag{21}$$

*then E is GAS.*

**Remark.** In [5] it was given the criterion  $a(2b + \phi) > 1$  which is, of course, more restrictive than (21)

Furthermore, from Propositions (2.5) and (2.6), it holds the following:

**Proposition 3.2.** *If  $c < c_1$  and*

$$c^2 < \frac{a^2 b^2}{\phi^2} (3\phi + 4b)(1 + a(\phi + 2b)) \tag{22}$$

*the equilibrium E is GAS.*

**Proof.** In the case of Zhang et al. model

$$N(u, v) = 2\phi uv - (3\phi + 4b)u^2 - 1 - a(\phi + 2b).$$

$N(u, v)$  change sign only on the hyperbole.

$$v = \frac{1}{2\phi} \left( (3\phi + 4b)u + \frac{1 + a(\phi + 2b)}{u} \right), \tag{23}$$

which has the minimum  $v_m = \frac{\sqrt{3\phi+4b}\sqrt{1+a(\phi+2b)}}{\phi}$ . In order to exclude closed paths in  $\Gamma$ , we may impose  $v_m > \frac{c}{ba}$ , which leads to

$$c^2 \frac{\phi^2}{b^2} < a^2(3\phi + 4b)(1 + a(\phi + 2b)).$$

Note that since  $P(c\frac{\phi}{b}) > 0$ , it is:  $u_e^2 < c^2 \frac{\phi^2}{b^2}$  and also

$$a^2(3\phi + 4b)(1 + a(\phi + 2b)) < u_M^2 = -a + \frac{4a}{1 + \sqrt{1 - 8a(\phi + 2b)}}$$

(as it is easy to see by setting  $x = 8a(\phi + 2b)$ ) i.e. when (22) condition holds automatically also  $c < c_1$  holds and  $E$  is GAS.  $\square$

**Remark.** In [5] the following GAS criterion is given:  $c^2 < \frac{a^2 b^2}{\phi^2} \frac{\phi}{2} (1 + a(\phi + 2b))$ , which is more restrictive than the one proposed here, since  $\frac{\phi}{2} < 3\phi + 4b$ .

For which regards the Hopf's bifurcation, the criterion becomes  $u_e \neq \sqrt{3a}$ .

For which regards the uniqueness of limit cycle, it has been impossible to apply the Zhang's theorem since it results that  $f(u)/g(u)$  is not increasing. On the contrary, some uniqueness results were found by applying a theorem of [7] through a remark in [8] which we rewrite by using our notation:

**Theorem 3.3.** *Suppose that for given parameter the system (2) is such that:*

1. *There exist  $u_2, u_1$  such that  $F(u_1) = F(u_2) = F(u_e) = 0$  (observe that it is:  $0 < u_2 < u_M < u_e < u_1 < c/(ba)$  and  $F'(u_M) = f(u_M) = 0$ ) and let it be*  

$$G(u_M) \leq G(u_1) \leq G(u_2).$$

- 2.  $(u - u_e)F(u) \leq 0$  for  $u \in (u_2, u_1)$ ;
- 3.  $F(u) \neq 0$  for small but non-zero  $u$ ;
- 4. The function

$$F(u) \frac{f(u)}{g(u)}$$

is non decreasing

then it has at most an unique and stable limit cycle.

For example for the following values of the parameters  $a = 0.01$ ,  $b = 1.1$ ,  $\varphi = 2.1$  we obtained that for  $c \in [0.168, 0.205]$  the uniqueness conditions required by (3.3) are fulfilled and there is a globally stable limit cycle. We stress out that the above result may be obtained near integrally through analytical calculations and no simulation

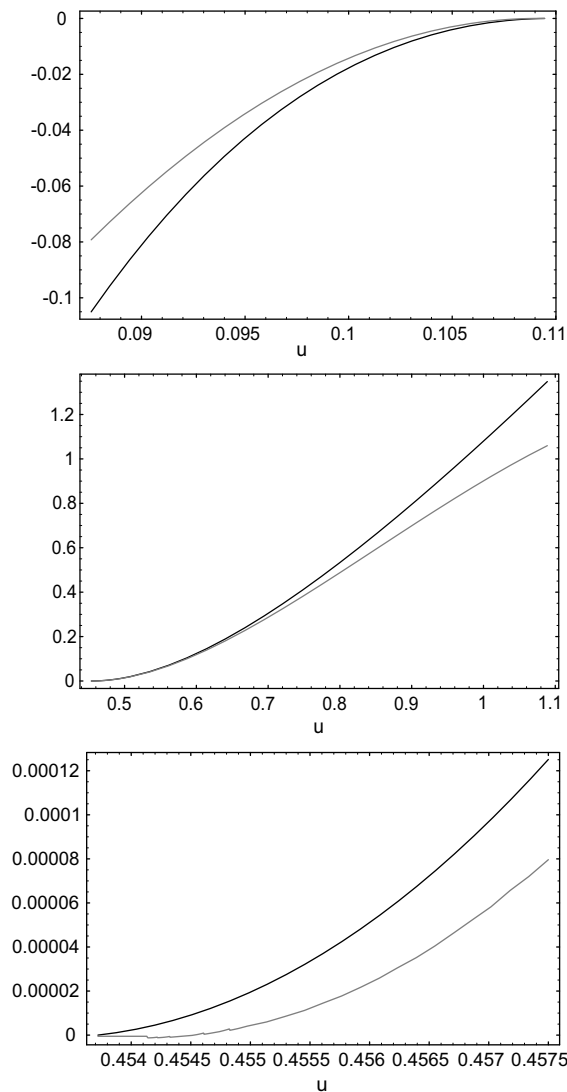


Fig. 1. High: plot of  $F(s)$  and of  $F(Z1(s))$  (in grey) for  $c = 0.064 \approx c_1$ : there is no intersection between the two curves. Medium: plot of  $F(s)$  and of  $F(Z2(s))$  (in grey) for  $c = 0.415 \approx c_2$ . Low: zoom of the central plot. Values of the other parameters:  $a = 0.01$ ,  $b = 1.1$ ,  $\varphi = 2.1$ .

of the differential model is needed. This result on uniqueness (and GAS) of the limit cycle is interesting, but it shows clearly that the used theorem is quite restrictive, since the range of  $c$  which guarantees the GAS of the limit cycle is small in comparison with  $(c_1(a, b, \varphi), c_2(a, b, \varphi))$  which is, in this case, such that  $(c_1, c_2) \approx (0.064, 0.414)$ . On the contrary, all our numerical simulations suggest that the GAS of the cycles holds in all the interval  $(c_1, c_2)$ . Furthermore, applying Proposition 2.7 we obtained that  $E$  is gas for  $c < c_1$  and for  $c > c_2$  (see Fig. 1).

Since periodic perturbations of systems having limit cycles a classical topic of bifurcation and chaos theory, and since the parameters may exhibit periodically varying dynamics, we performed some numerical simulations (by using directly 2, of course) by assuming that

$$c = c(t) = C_0(1 + d \cos(\omega t)), \quad 1 > d > -1. \quad (24)$$

In effect, in such a case the dynamics become very rich with period doublings and “ $n$ -ings”, and transitions to quasi periodicity. With reference to Fig. 2, where  $\omega$  is the bifurcation parameter and  $d = 0.9$ , we notice that the values  $\omega = \omega_0, 2\omega_0, 3\omega_0$  corresponds to solutions having period  $T_0$  since they lies in the ranges where there is one, two and three points in the bifurcation diagram.

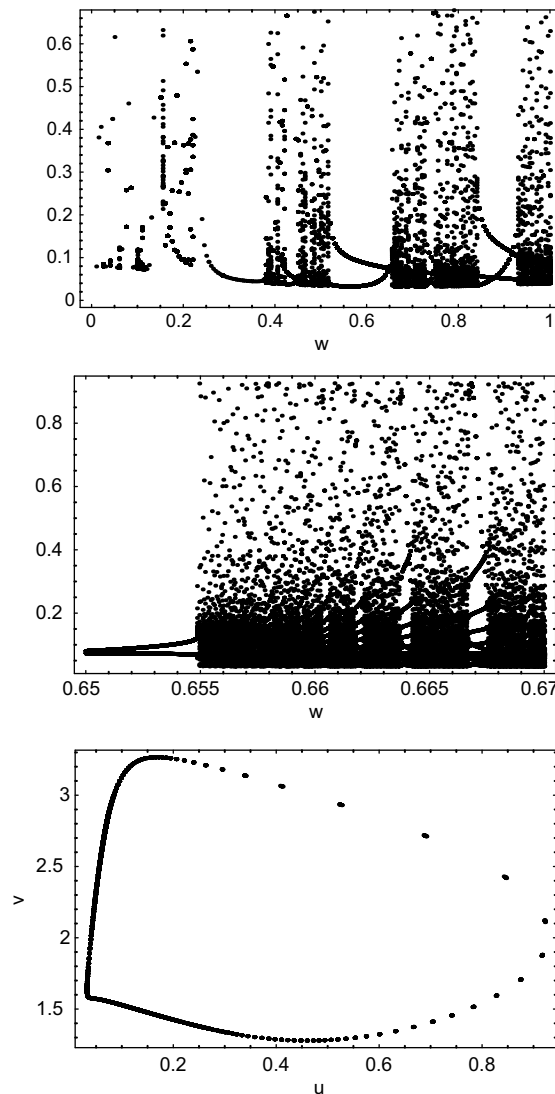


Fig. 2. High: bifurcation diagram with  $\omega$  as bifurcation parameter and  $d = 0.90$ . Medium: zoom of the above diagram for  $\omega \in (0.65, 0.67)$ . Low: Poincaré's plot for  $\omega = 0.665$  and  $d = 0.9$ .

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