Dynamics of a 3 cluster cell-cycle system with positive linear feedback.

Bastien Fernandez* and Todd R. Young†

Abstract

In this technical note we calculate the dynamics of a linear feedback model of progression in the cell cycle in the case that the cells are organized into \( k = 3 \) clusters. We examine the dynamics in detail for a specific subset of parameters with non-empty interior.

There is an interior fixed point of the Poincaré map defined by the system. This fixed point corresponds to a periodic solution with period \( T \) in which the three clusters exchange positions after time \( T/3 \). We call this solution 3-cyclic. In all the parameters studied, the fixed point is either:

• isolated and locally unstable, or,
• contained in a neutrally stable set of period 3 points.

In the later case the edges of the neutrally stable set are unstable. This case exists if either the three clusters are isolated from each other, or, if they interact in a non-essential way. In both cases the orbits of all other interior points are asymptotic to the boundary. Thus 3-cyclic solutions are practically unstable in the sense the arbitrarily small perturbations may lead to loss of stability and eventual merger of clusters. Since the single cluster solution (synchronization) is the only solution that is asymptotically stable, it would seem to be the most likely to be observed in application if the feedback is similar to the form we propose and is positive.

January 20, 2013.

1 Introduction

This technical note is a supplement to the manuscript [1]. In that work the dynamics of cells in a cell cycle were considered when cells are subjected to feedback from other cells in the cell cycle and the response to the feedback is also dependent on the cells location

*Centre de Physique Théorique (UMR 6207 CNRS - Université Aix-Marseille II - Université Aix-Marseille I - Université Sud Toulon-Var) CNRS Luminy Case 907, 13288 Marseille CEDEX 9, France
†Corresponding author. 321 Morton Hall, Mathematics, Ohio University, Athens, OH 45701, USA, young@math.ohiou.edu
within the cell cycle. We refer the reader to that manuscript for the biological motivation for this study and for background on the model we study.

We consider a piecewise affine model for the dynamics of cell populations along the cell cycle. Let a population of $N$ cells be organized in $k$ equal clusters ($k$ divides $N$) labeled by a discrete index $i \in \{0, \ldots, k - 1\}$. For the cluster $i$, the progression along the cycle is represented by the periodic variable $x_i \in \mathbb{R}/\mathbb{Z}$ which evolves in time according to the entire population status. More specifically, the variables follow the deterministic flow associated with a real vector field $f$, i.e. $\dot{x}_i = f_i(x_i, \bar{x}, r, s), \quad i = 0, \ldots, k - 1$, that is the same for each $i$. Here $0 < s \leq r < 1$ are two parameters respectively governing the length of the signaling $S = [0, s) + \mathbb{Z}$ and of the responsive $R = [r, 1) + \mathbb{Z}$ regions. Let $\sigma$ represent the fraction of cells in the signaling region, i.e.

$$\sigma = \frac{\# \{ j : x_j \in [0, s) \text{ mod } 1 \} }{k}.$$ 

Then we will consider the case that $f$ assumes a simple expression

$$\frac{dx_i}{dt} = f_i(\bar{x}, r, s) = \begin{cases} 1 & \text{ if } x_i - \lfloor x_i \rfloor \in [0, s) \\ 1 + \sigma & \text{ if } x_i - \lfloor x_i \rfloor \in [r, 1), \end{cases}$$

where $\lfloor \cdot \rfloor$ denotes the floor function. In short terms, clusters in the responsive region are accelerated by a fraction equal to the proportion of cells in the signaling region. In [1] we consider systems in which the feedback experienced by cells $R$ is a general monotone increasing or decreasing function of $\sigma$.

Relabeling, integer translation of coordinates, and time translation are symmetries of the dynamics. Thus, one can assume that all coordinates $x_i(0)$ are initially well-ordered and belong to the same unit interval, i.e. we have

$$0 = x_0(0) \leq x_i(0) \leq x_{k - 1}(0) < 1, \quad i = 1, \ldots, k - 2.$$ 

The definition of the vector field $f$ implies that the coordinates cannot cross each other as time evolves; thus this ordering is preserved under the dynamics. Moreover, the first coordinate $x_0$ must eventually reach 1 (not later than at time 1), i.e. there exists $t_R \leq 1$ such that $x_0(t_R) = 1$, and more generally, it must reach any positive integer as time runs. Thus the set $x_0 \in \mathbb{N}$ defines a Poincaré section for the dynamics and the mapping

$$(x_1(0), x_2(0), \ldots, x_{k - 1}(0)) \mapsto (x_1(t_R), x_2(t_R), \ldots, x_{k - 1}(t_R))$$

defines the corresponding return map.

We rely on the following considerations. Starting from $t = 0$, compute the time $t_1$ that $x_{k - 1}$ needs to reach 1 and compute the location of the remaining cells at this date. Define $F$ to be this mapping. (We assume first that $x_{k - 2}(t_1) < 1$ for simplicity, but we will relax this soon.)

$$F : (x_1(0), x_2(0), \ldots, x_{k - 1}(0)) \mapsto (x_0(t_1), x_1(t_1), \ldots, x_{k - 2}(t_1))$$

2
Figure 1: Illustration of the map $F$ for $k = 3$. Here $F(x_1, x_2) = (x'_1, x'_2) = (x_0(t_1), x_1(t_1))$.

Notice that $x_0(t_1) = t_1$ by assumption on $x_0(0)$.

Now the time $t_1 + t_2$ that $x_{k-2}$ needs to reach 1, together with the population configuration at $t = t_1 + t_2$, follow by applying $F$ to the configuration $(x_0(t_1), x_1(t_1), \ldots, x_{k-2}(t_1))$. By repeating the argument, the desired return time $t_R$ is given by $t_R = t_1 + t_2 + \cdots + t_k$ and the desired return map is $F^k$. Therefore, to understand the dynamics, one only has to compute the first map $F$.

1.1 General properties for arbitrary $k$

It was noted in [1] that we may regard $F$ as a continuous piecewise affine map of the $(k-1)$-dimensional simplex

$$0 \leq x_1 \leq x_2 \leq \ldots \leq x_{k-1} \leq 1$$

into itself. (Although the boundaries 0 and 1 are identified in the original flow, in the analysis here, we consider them as being distinct points for $F$.)

On the edges of the simplex, $F$ has a relatively simple dynamics. Indeed if, initially, all coordinates are equal, then they must all reach the boundary 1 simultaneously. In other words, on the diagonal ($x_i = x$ for all $i$), we have $F(x, \ldots, x) = (t_1, 1, \ldots, 1)$ where $t_1$ depends on $r, s$ and $x$ (for $x = 0$, we have $t_1 = 1$ independently of $r$ and $s$). Moreover, starting with $x_{k-1} = 1$ implies $t_1 = 0$ which yields

$$F(x_1, \ldots, x_{k-2}, 1) = (0, x_1, \ldots, x_{k-2})$$

whatever the remaining coordinates $x_1, \ldots, x_{k-2}$ are. As a consequence, the edge

$$\{(x, 1, \ldots, 1) : x \in [0, 1]\}$$

is mapped onto

$$\{(0, x, 1, \ldots, 1) : x \in [0, 1]\}$$

which is mapped onto $\{(0, 0, x, 1, \ldots, 1) : x \in [0, 1]\}$ and so on, until it reaches the edge $(0, \ldots, 0, x)$ which is mapped back onto the diagonal (after $k$ iterations).

A particular orbit on the edges is the $k$-periodic orbit passing the vertices, and which corresponds to the single cluster of velocity 1 in the original flow, namely

$$(0, \ldots, 0) \mapsto (1, \ldots, 1) \mapsto (0, 1, \ldots, 1) \mapsto (0, 0, 1, \ldots, 1) \mapsto \ldots \mapsto (0, \ldots, 0, 1) \mapsto (0, \ldots, 0)$$
From a direct analysis in the original system [1], we know that this orbit must be asymptotically stable for positive feedback and unstable for negative. Since there are two points of a periodic orbit at each boundary of every edge (which are themselves globally $k$-periodic 1-dimensional sets), by the intermediate value theorem, there must be at least one other $k$-periodic orbit on the edges with coordinates comprised between 0 and 1. Whether this orbit is unique might depend on parameters.

Finally, since the simplex is a convex and compact invariant set under $F$ and the boundary cannot contain any fixed point, the Brouwer fixed point theorem implies the existence of a fixed point in its interior. From the definition of $F$ this corresponds to a solution satisfying:

$$x_i(t_1) = x_{i+1}(0) \text{ for all } i = 0, \ldots, k - 2, \text{ and } x_{k-1}(t_1) = x_0(0) \mod 1. \quad (1.1)$$

We call this type of solution a $k$-cyclic solution [1].

2 Dynamics for $k = 3$

We will study the dynamics of the linear model only for a limited subset of parameter space. It will become clear to the reader that the analysis could be reproduced for the entire parameter space, but doing so would require a prohibitive amount of time and space.

2.1 Computation of the map $F$

When $k = 3$, $F$ is defined in the triangle $0 \leq x_1 \leq x_2 \leq 1$ and maps the pair $(x_1, x_2)$ into $(t_1, x_1(t_1))$, i.e. not only the hitting time $t_1$ needs to be computed now, but also the location of $x_1$ at this instant has to be specified. There are numerous cases to study depending on $x_1$ and $x_2$. To list them, we primarily use the location of $x_2$.

- $0 \leq x_2 < r - s$. As for $k = 2$, in this case $x_2$ moves with velocity 1, even when lying in $R$. Therefore $t_1 = 1 - x_2$. Since $x_1 \leq x_2$, we also have $x_1 \leq r - s$ and thus $x_1(t_1) = x_1 + t_1 = 1 - x_2 + x_1$.

- $r - s \leq x_2 < r$. In this case, $x_2$ enters the responsive region, but only after a while, precisely at $t = r - x_2$. Its acceleration depends on the location of $x_1$ at this date, whether $x_1$ belongs to $S$ or not. This alternative is given by the relative sizes of $r - x_2$ and $s - x_1$. Considering also the possible cases of acceleration for $x_1$ we get the following sub-cases. For simplicity, we assume that $s < r - s$ and $r + \frac{5}{3}s < 1$.

  * $0 \leq x_1 \leq s$ and $0 < r - x_2 < s - x_1$. In this case, $x_1$ is still in $S$ when $x_2$ enters $R$. The assumption $r + \frac{5}{3}s < 1$ implies that both $x_0$ and $x_1$ get out of $S$ before
$x_2$ reaches 1 (existence of the third line in the expression below). We then have

$$x_2(t) = \begin{cases} 
  r + \frac{5}{3}(t - r + x_2) & \text{if } r - x_2 < t \leq s - x_1 \\
  r + \frac{5}{3}(s - x_1 - r + x_2) + \frac{4}{3}(t - s + x_1) & \text{if } s - x_1 < t \leq s \\
  r + \frac{2}{3}t & \text{if } s < t
\end{cases}$$

which implies $t_1 = 1 - \frac{5}{3}x_2 + \frac{x_1}{3} + \frac{2}{3}(r - s)$. Furthermore, the assumption $s < r - s$ forces $x_0(t)$ to be out of $S$ when $x_1(t)$ enters $R$ (if it does). Then $x_1(t_1) = x_1 + t_1$
in this case.

* $0 \leq x_1 \leq s$ and $s - x_1 \leq r - x_2 \leq s$ or $s < x_1 \leq r - s$ and $x_2 < r$. Here, $x_1(t)$ is out of $S$ when $x_2(t)$ enters $R$. From parameter assumptions we have $r + \frac{5}{3}s < 1$ and thus $x_0$ leaves $S$ before $x_2$ reaches 1. Consequently, the evolution of $x_2$ reads

$$x_2(t) = \begin{cases} 
  r + \frac{5}{3}(t - r + x_2) & \text{if } r - x_2 < t \leq s \\
  r + \frac{2}{3}(s - r + x_2) + t - s & \text{if } s < t
\end{cases}$$

from which we get $t_1 = 1 - \frac{5}{3}x_2 + \frac{2}{3}s$ and again $x_1(t_1) = x_1 + t_1$.

* $r - s < x_1 \leq x_2$ and $r - s < x_2 < r$. In this case, $t_1$ remains as before. However, $x_1$ now suffers some acceleration and we have

$$x_1(t) = \begin{cases} 
  r + \frac{5}{3}(t - r + x_1) & \text{if } r - x_1 < t \leq s \\
  r + \frac{2}{3}(s - r + x_1) + t - s & \text{if } s < t
\end{cases} \quad (2.1)$$

Consequently $x_1(t_1) = 1 - \frac{5}{3}(x_2 - x_1)$.

* $r \leq x_2$ and $0 \leq x_1 \leq s$. For $x_2$ larger than $r$ it is useful to consider separately the cases $x_1 \leq s$ and $x_1 > s$. In the latter case, we always have $x_1(t_1) = x_1 + t_1$ but the expression of $t_1$ depends on $x_2$. We have 3 sub-cases

* $0 \leq x_1 \leq s$ and $r \leq x_2 \leq 1 - \frac{5}{3}s + \frac{x_1}{3}$. Here $x_2$ starts sufficiently near 0 so that both $x_1$ and $x_0$ get out of $S$ before $t_1$

$$x_2(t) = \begin{cases} 
  x_2 + \frac{5}{3}t & \text{if } 0 < t \leq s - x_1 \\
  x_2 + \frac{5}{3}(s - x_1) + \frac{4}{3}(t - s + x_1) & \text{if } s - x_1 < t \leq s \\
  x_2 + \frac{5}{3}s - \frac{2}{3}t & \text{if } s < t
\end{cases}$$

which implies $t_1 = 1 - x_2 + \frac{x_1}{3} - \frac{2}{3}s$.

* $0 \leq x_1 \leq s$ and $1 - \frac{5}{3}s + \frac{2}{3}s < x_2 \leq 1 - \frac{5}{3}(s - x_1)$. In this case, we have $t_1 \leq s$ and hence $x_2$ reaches 1 during the second phase in the previous expression. This yields $t_1 = \frac{2}{3} \left( 1 - x_2 + \frac{2}{3}t - \frac{2}{3}s \right)$.

* $0 \leq x_1 \leq s$ and $1 - \frac{5}{3}(s - x_1) \leq x_2 \leq 1$. There $x_2$ reaches 1 even before $x_1$ reaches $s$. This results in $t_1 = \frac{2}{5}(1 - x_2)$. 


• $s < x_1$. When $x_1 > s$, the situation for $x_2$ is similar to as for $k = 2$. This point may reach 1 before or after $x_0$ leaves $S$. The first case occurs when $r \leq x_2 \leq 1 - \frac{4}{3}s$ and gives $t_1 = 1 - x_2 - \frac{s}{3}$. In the second case $1 - \frac{1}{3}s < x_2 \leq 1$, we have $t_1 = \frac{3}{4}(1 - x_2)$.

We can now focus on $x_1(t_1)$. When $r \leq x_2 < 1 - \frac{4}{3}s$ and $x_1 \leq r - s$, there cannot be any acceleration and thus $x_1(t_1) = x_1 + t_1$. Furthermore, when $1 - \frac{1}{3}s \leq x_2 \leq 1$, we have $t_1 < s$ and thus $x_1$ receives any acceleration only if it is initially larger than $r - t_1$. In practice, this leads the following cases.

• $r - s < x_1 < r$ and $r \leq x_2 < 1 - \frac{4}{3}s$. In this case, $s < t_1$ and the evolution of $x_1$ is as in equation (2.1). It results that $x_1(t_1) = 1 - x_2 + \frac{4}{3}x_1 - \frac{s}{3}$.

• $r - \frac{3}{4}(1 - x_2) < x_1 < r$ and $1 - \frac{4}{3}s \leq x_2 \leq 1$, then only the first phase in (2.1) applies and we get again $x_1(t_1) = 1 - x_2 + \frac{4}{3}x_1 - \frac{r}{3}$.

• $r \leq x_1 < x_2$ and $r \leq x_2 < 1 - \frac{4}{3}s$. Now, we have

$$x_1(t) = \begin{cases} x_1 + \frac{4}{3}t & \text{if } t \leq s \\ x_1 + \frac{4}{3}s + t - s & \text{if } s \leq t \end{cases}$$

Thus $x_1(t_1) = x_1 + t_1 + \frac{s}{3} = 1 - x_2 + x_1$.

• $r \leq x_1 < x_2$ and $1 - \frac{4}{3}s < x_2 \leq 1$. As $t_1 < s$, only the first phase applies in the previous expression. We get $x_1(t_1) = 1 - x_2 + x_1$.

All together, when the parameters are such that $2s < r < 1 - \frac{5}{3}s$, the triangle decomposes into 13 polygonal subdomains with affine dynamics, see Figure 2. For simplicity, we have labeled these domains by integer numbers following the increasing ordering in the coordinates $x_1$ and then in $x_2$. For the sake of clarity, we provide the following table that recapitulates the domains and the corresponding expression of $F$. Since the map $F$ is continuous (but not $C^1$), the expressions coincide on the domain boundaries. Accordingly, (when stability is not considered) boundaries can be regarded as simultaneously belonging the adjacent domains.
Figure 2: $k = 3$. Partition of the triangle $0 \leq x_1 \leq x_2 \leq 1$ and its image under $F$ for the pair $(r, s) = (\frac{5}{12}, \frac{1}{8})$ chosen such that $2s < r \leq \frac{1}{2} - \frac{s}{3}$.

| Label | Condition on $x_1$ | Condition on $x_2$ | $x_0(t_1)$ | $x_1(t_1)$ |
|-------|---------------------|---------------------|-------------|-------------|
| 1     | $0 \leq x_1 \leq x_2$ | $0 \leq x_2 < r - s$ | $1 - x_2$ | $1 - x_2 + x_1$ |
| 3a    | $0 \leq x_1 \leq s$ | $r - s \leq x_2 < r - s + x_1$ | $1 - \frac{4s}{3} - \frac{r-s}{3}$ | $1 - \frac{4s}{3} + x_1 + \frac{r-s}{3}$ |
| 2     | $0 \leq x_1 \leq s$ | $r - s + x_1 \leq x_2 < r$ | $1 - \frac{5s-x_1}{3} + \frac{2(r-s)}{3}$ | $1 - \frac{5s-x_1}{3} + \frac{2(r-s)}{3}$ |
| 5     | $0 \leq x_1 \leq s$ | $r \leq x_2 < 1 - \frac{x_1}{3} + \frac{2s}{3}$ | $1 - x_2 + \frac{x_1}{3} - \frac{2s}{3}$ | $1 - x_2 + \frac{x_1}{3} - \frac{2s}{3}$ |
| 10    | $0 \leq x_1 \leq s$ | $1 - \frac{5s-x_1}{3} \leq x_2 < 1 - \frac{3s-x_1}{3}$ | $\frac{3(1-x_2)}{4} + \frac{x_1-s}{4}$ | $\frac{3(1-x_2)}{4} + \frac{5s-x_1}{4}$ |
| 9     | $0 \leq x_1 \leq s$ | $1 - \frac{4s-x_1}{3} \leq x_2 \leq 1$ | $\frac{3(1-x_2)}{5}$ | $\frac{3(1-x_2)}{5}$ |
| 3b    | $s \leq x_1 \leq r - s$ | $r - s \leq x_2 < r$ | $1 - \frac{4s}{3} + \frac{x_1}{3}$ | $1 - \frac{4s}{3} + x_1 + \frac{x_1}{3}$ |
| 6     | $s \leq x_1 \leq r - s$ | $r \leq x_2 < 1 - \frac{x_1}{3}$ | $1 - x_2 - \frac{x_1}{3}$ | $1 - x_2 + x_1 - \frac{x_1}{3}$ |
| 11    | $s \leq x_1 \leq r - \frac{3(1-x_2)}{4}$ | $1 - \frac{4s}{3} \leq x_2 \leq 1$ | $\frac{3(1-x_2)}{4}$ | $\frac{3(1-x_2)}{4}$ |
| 4     | $r - s \leq x_1 \leq x_2$ | $r - s \leq x_2 < r$ | $1 - \frac{4s}{3} + \frac{r-s}{3}$ | $1 - \frac{4s}{3} + x_1 + \frac{r-s}{3}$ |
| 7     | $r - s \leq x_1 \leq r$ | $r \leq x_2 \leq 1 - \frac{4s}{3}$ | $1 - x_2 - \frac{r-s}{3}$ | $1 - x_2 + \frac{x_1}{3} - \frac{r}{3}$ |
| 12    | $r - \frac{3(1-x_2)}{4} \leq x_1 \leq r$ | $1 - \frac{4s}{3} \leq x_2 \leq 1$ | $\frac{3(1-x_2)}{4}$ | $\frac{3(1-x_2)}{4}$ |
| 8     | $r \leq x_1 \leq x_2$ | $r \leq x_2 \leq 1 - \frac{4s}{3}$ | $1 - x_2 - \frac{r-s}{3}$ | $1 - x_2 + x_1$ |
| 13    | $r \leq x_1 \leq 1$ | $1 - \frac{4s}{3} \leq x_2 \leq 1$ | $\frac{3(1-x_2)}{4}$ | $\frac{3(1-x_2)}{4}$ |

2.2 The symbolic dynamics

In order to obtain insights into the dynamics, we study the image of the triangle partition by using explicit expressions in the table above. To that goal, we begin with a series of elementary observations.

- We already know from the analysis for arbitrary $k$ that the 3 corner points are mapped one into another in a stable period-3 orbit. We also know that there must be another
3-periodic orbit on the edges.

- In addition, there must be a fixed point inside the triangle.
- \( F(a) = F(0, r - s) = (1 - r + s, 1 - r + s) \) and \( F(b) = F(r - s, r - s) = (1 - r + s, 1) \). So the horizontal segment \((a, b)\) is mapped into a vertical one with abscissa \(1 - r + s\). Depending on the location of \( r \) in the interval \([2s, 1 - \frac{5s}{3}]\), the quantity \(1 - r + s\) varies in the interval \([s, 1]\). Precisely, we have (one or several cases might not apply depending on \( s \))

| Conditions on \((r, s)\) | Location of the segment \([F(a), F(b)]\) |
|--------------------------|------------------------------------------|
| \(2s \leq r \leq \frac{1+s}{2}\) | beyond \( r \) |
| \(\frac{1+s}{2} < r \leq \frac{1}{2} + s\) | between \( r - s \) and \( r \) |
| \(\frac{1}{2} + s < r \leq 1 - \frac{5s}{3}\) | between \( s \) and \( r - s \) |

- Similarly, the segment \((d, e, f)\) is mapped into a vertical one since we have \( F(d) = F(s, r) = (1 - r - \frac{2s}{3}, 1 - r + \frac{2s}{3}) \), \( F(e) = F(r - s, r) = (1 - r - \frac{s}{3}, 1 - \frac{4s}{3}) \) and \( F(f) = F(r, r) = (1 - r - \frac{4s}{3}, 1) \). The parameter dependent location of \(1 - r - \frac{4s}{3}\) is listed in the following table

| Conditions on \((r, s)\) | Location of the segment \([F(d), F(f)]\) |
|--------------------------|------------------------------------------|
| \(2s \leq r \leq \frac{1}{2} - \frac{5s}{3}\) | beyond \( r \) |
| \(\frac{1}{2} - \frac{5s}{3} < r \leq \frac{1}{2} + \frac{s}{3}\) | between \( r - s \) and \( r \) |
| \(\frac{1}{2} + \frac{s}{3} < r \leq 1 - \frac{5s}{3}\) | between \( s \) and \( r - s \) |

- We already know that the segment \((l, m)\) is mapped onto the vertical axis \( x_1 = 0 \). Moreover \( F(l) = (0, r) = (1 - r - \frac{2s}{3}, 1 - r - \frac{2s}{3}) \).

The two previous properties imply that the regions in the upper vertical strip are mapped into the following ones (see Figure 2)

- \(9, 10 \mapsto 1\)
- \(11 \mapsto 1 \cup 2 \cup 3\)
- \(12 \mapsto 5\)
- \(13 \mapsto 5 \cup 10 \cup 9\)

For the remaining regions, the situation depends on parameters and decomposes in various cases according to the two previous tables. We consider here the case where all points from
a to \( f \) fall beyond the vertical line \( x_1 = r \), \textit{i.e.} \( 2s < r < \frac{1}{2} - \frac{s}{3} \). From Figure 2 we get the following properties

\[
\begin{align*}
1, 2, 3, 4 & \rightarrow 8 \cup 13 \\
5, 6 & \rightarrow 1 \cup 3 \cup 4 \cup 6 \cup 7 \cup 8 \\
7 & \rightarrow 6 \cup 7 \cup 8 \cup 13 \\
8 & \rightarrow 6 \cup 7 \cup 11 \cup 12 \cup 13
\end{align*}
\]

### 2.3 Parameter dependence of fixed points and bifurcations

The above properties suggest to consider possible fixed points in 6 and in 7. It turns out more convenient to study the one in 7 and to follow its bifurcations in parameter space.

**Fixed point in 7:** The (unique) fixed point in 7, namely \((\frac{3 + r - 2s}{10}, \frac{21 - 3r - 4s}{30})\) turns out to be a source (with associated complex eigenvalues for \( F^3 \) - the return map under study) which exists provided that

\[
\frac{3 - 2s}{9} < r < \frac{3 + 8s}{9}
\]

At the lower boundary \( r = \frac{3 - 2s}{9} \) of this domain, the first coordinate meets the vertical boundary with 8. This suggests that \((\frac{3 + r - 2s}{10}, \frac{21 - 3r - 4s}{30})\) might be continued as a fixed point in 8 for \( r < \frac{3 - 2s}{9} \). This is indeed the case.

- **Fixed point in 8:** Easy calculations conclude that the coordinates are given by \((\frac{3 - 2s}{9}, \frac{6 - s}{9})\). Moreover, the fixed point is neutral (with a double eigenvalue of \( F^3 \) equal to 1) and it exists provided that

\[
2s < r < \frac{3 - 2s}{9}
\]

For \( r = \frac{3 - 2s}{9} \) this point coincides with the fixed point in 7 and we expect a kind of pitchfork bifurcation which would create a 3-periodic orbit with code 7 \( \rightarrow \) 7 \( \rightarrow \) 8 \( \rightarrow \) 7.

- **Period-3 orbit 7 \( \rightarrow \) 7 \( \rightarrow \) 8 \( \rightarrow \) 7:** Calculations show that this (unique) orbit has coordinates:

\[
(r, 1 - r - \frac{s}{3}) \mapsto (r, 2r + \frac{s}{3}) \mapsto (1 - 2r - \frac{2s}{3}, 1 - r - \frac{s}{3}) \mapsto (r, 1 - r - \frac{s}{3})
\]

and indeed emerges from the fixed point in 7 at \( r = \frac{3 - 2s}{9} \). It persists for all lower values of \( r \) down to 2s and is expanding with double real eigenvalues.

- **Period-3 orbits 8 \( \rightarrow \) 8 \( \rightarrow \) 8 \( \rightarrow \) 8:** Topological considerations suggest that other orbits should come into play at \( r = \frac{3 - 2s}{9} \). Indeed, calculations confirm that a two-parameter family of 3-periodic orbits lying in 8 also emerges from the fixed point in 7 when \( r \) crosses \( \frac{3 - 2s}{9} \) downward. All orbits are neutral with double eigenvalue 1 and their coordinates have the following expressions

\[
(x_1, x_2) \mapsto (1 - x_2 - \frac{s}{3}, 1 - x_2 + x_1) \mapsto (x_2 - x_1 - \frac{s}{3}, 1 - \frac{s}{3} - x_1) \mapsto (x_1, x_2)
\]
Figure 3: Invariant triangle composed of the neutral fixed point and neutral period 3 orbits lying in 8. The 3 corners are points of the 3-periodic orbit with code $7 \mapsto 7 \mapsto 8 \mapsto 7$. Notice that the left vertical edge (belongs to 8 and) is part of the boundary between 7 and 8.

where $x_1$ is arbitrary in the interval $(r, x_2 - r - \frac{s}{3})$, $x_2$ is arbitrary in $(2r + \frac{s}{3}, 1 - r - \frac{s}{3})$ and $r$ is arbitrary in $[2s, \frac{3-2s}{9}]$. The orbits can be viewed as rotating around the fixed point $(\frac{3-2s}{9}, \frac{6-s}{9})$ which is included in the family (i.e. for $(x_1, x_2) = (\frac{3-2s}{9}, \frac{6-s}{9})$, the orbit actually reduces to a fixed point). The closure of the set of orbit coordinates forms a triangle whose corners are the coordinates of the orbit $7 \mapsto 7 \mapsto 8 \mapsto 7$ (see Figure 3).

At the upper boundary $r = \frac{3+8s}{9}$ of the “7”-fixed point’s existence domain, its first coordinate meets the vertical boundary with 6. We then consider the fixed point in 6.

- **Fixed point in 6:** Its coordinates are given by $(\frac{3-s}{9}, \frac{2(3-s)}{9})$ and this neutral fixed point exists iff

$\frac{3+8s}{9} \leq r \leq \frac{2(3-s)}{9}$

The bifurcation scenario at $r = \frac{3+8s}{9}$ is similar to the one above at the lower boundary $r = \frac{3-2s}{9}$.

- **Period-3 orbit $7 \mapsto 7 \mapsto 6 \mapsto 7$:** It turns out that this unique orbit emerges from the fixed point 7 at $r = \frac{3+8s}{9}$ and exists up to $r = \frac{3+2s}{6}$ (or up to $1 - \frac{5s}{3}$ whichever is smaller). It is expanding with double real eigenvalues. At $r = \frac{3+2s}{6}$ both the component in 6 and its successor cross the horizontal line $x_2 = r$ and the second component in 7 cross the upper domain boundary $x_2 = 1 - \frac{4s}{3}$.

However, the value $r = \frac{3+2s}{6}$ does not involve any existence condition related to the fixed point in 6. As shown below, the reason is that the periodic orbit can be continued up to $\frac{2(3-s)}{9}$ provided that we consider the appropriate sequence of symbols.
• Period-3 orbit 6 $\mapsto$ 3 $\mapsto$ 3 $\mapsto$ 6: This orbit continues the orbit 7 $\mapsto$ 7 $\mapsto$ 6 $\mapsto$ 7 when $r > \frac{3+2s}{6}$. Indeed, it exists provided that

$$\frac{3+2s}{6} \leq r \leq \frac{2(3-s)}{9}$$

It is expanding with 2 real eigenvalues (the same as those associated with 7 $\mapsto$ 7 $\mapsto$ 6 $\mapsto$ 7) and coincide with 7 $\mapsto$ 7 $\mapsto$ 6 $\mapsto$ 7 at $r = \frac{3+2s}{6}$.

• Period-3 orbits 6 $\mapsto$ 6 $\mapsto$ 6 $\mapsto$ 6: Similarly to as before, a triangle of neutral 3-periodic orbits is created from the fixed point 7 at $r = \frac{3+8s}{9}$. The coordinates have the following expression

$$(x_1, x_2) \mapsto (1 - x_2 - \frac{s}{3}, 1 - x_2 + x_1 - \frac{s}{3}) \mapsto (x_2 - x_1, 1 - x_1 - \frac{s}{3}) \mapsto (x_1, x_2)$$

and these orbits exist in the same parameter domain as the fixed point in 6. When $r \in \left[\frac{3+8s}{9}, \frac{3+2s}{6}\right]$ the restrictions on coordinates are

$$1 - 2r + \frac{5s}{3} < x_1 < r - s \quad \text{and} \quad 1 - r + \frac{2s}{3} < x_2 < x_1 + r - s$$

and they are

$$2r + \frac{s}{3} - 1 < x_1 < 1 - r - \frac{s}{3} \quad \text{and} \quad r < x_2 < x_1 + 1 - r - \frac{s}{3}$$

when $r \in \left[\frac{3+2s}{6}, \frac{2(3-s)}{9}\right]$.

At the boundary $r = \frac{2(3-s)}{9}$, the expanding periodic orbit and the family of neutral orbits meet with the neutral fixed point “6” in an inverse pitchfork bifurcation to create the fixed point in 3.

• Fixed point in 3: The fixed point $\left(\frac{3r-s}{11}, \frac{2(3-r-s)}{11}\right) \in 3$ is expanding with double real eigenvalues and exists in the domain

$$\frac{2(3-s)}{9} \leq r \leq \frac{2}{3} + s$$

At the upper boundary $r = \frac{2}{3} + s$ of its existence domain, the fixed point ”3” meets the region 1.

• Fixed point in 1: The fixed point $\left(\frac{1}{3}, \frac{2}{3}\right)$ is neutral with double real eigenvalue 1 and exists in the domain

$$\frac{2}{3} + s \leq r < 1$$
Figure 4: \( k = 3 \). Parameters domains of existence of fixed points and related periodic orbits analyzed in this section. In regions (2) and (4) the unique fixed point is unstable. In regions (1), (3) and (5) the fixed point is neutral and sits inside a triangle of neutral period 3 points.

- **Period-3 orbit 3 \( \mapsto 3 \mapsto 1 \mapsto 3 \):** Same parameter domain. Expression of coordinates

  \[
  (2(r - s) - 1, r - s) \mapsto (1 - r + s, r - s) \mapsto (1 - r + s, 2(1 - r + s)) \mapsto (2(r - s) - 1, r - s)
  \]

  Expanding with double real eigenvalue. Emerges from the fixed point 3.

- **Period-3 orbit 1 \( \mapsto 1 \mapsto 1 \mapsto 1 \):** Same parameter domain. Triangle of neutral 3-periodic orbits

  \[
  (x_1, x_2) \mapsto (1 - x_2, 1 - x_2 + x_1) \mapsto (x_2 - x_1, 1 - x_1) \mapsto (x_1, x_2)
  \]

  where \( x_1 \) is arbitrary in \( (1 - r + s, 2(r - s) - 1) \) and \( x_2 \in (1 - r + s + x_1, r - s) \). As before, the corners coincides with the period-3 orbit 3 \( \mapsto 3 \mapsto 1 \mapsto 3 \).

To recapitulate, the return map \( F^3 \) possesses the following orbits depending on parameters in the considered regions (see Figure 4).

(1) \( 2s \leq r \leq \frac{3 - 2s}{9} \): three sources (two of them belong to 7, the other one lies in 8) and a two-parameter family of neutral fixed points lying inside the triangle whose corners are the 3 sources.

(2) \( \frac{3 - 2s}{9} < r \leq \frac{3 + 8s}{9} \): One source in 7.

(3) \( \frac{3 + 8s}{9} < r \leq \frac{2(3 - r)}{9} \): Similarly to as in (1); namely three sources (two in 7, one 6 if \( r \leq \frac{3 + 2s}{6} \), and two sources belong to 3 and one is in 6 for \( r \geq \frac{3 + 2s}{6} \)) and a triangle of neutral fixed points in 6.
\[2(3-s) < r \leq \frac{2}{3} + s.\] Similarly to as in (2); namely a single source in 1.

\[\frac{2}{3} + s < r < 1 - \frac{5s}{3}.\] Similarly to as in (1); namely three sources (two lie in 3 and 1 lies in 1) and a triangle of neutral fixed points in 1.

Note that in case (5) we have \(r - s > \frac{2}{3}\) and this corresponds to the case that the three clusters in the cyclic solution (which has initial conditions \((0, 1/3, 2/3)\) do not interact, i.e. \(x_0\) leaves \(S\) before \(x_2\) enters \(R\) and no feedback is experienced.

In the cases (1) and (3) the clusters in the cyclic solution experience feedback, but in a non-essential way, by which we mean that small perturbations do not lead either to further separation or contraction between the clusters. For instance in case (3) \(x_2\) begins in \(R\) and \(x_1\) begins in between \(S\) and \(R\) and \(x_0\) leaves \(S\) before either of these states changes. In case (1) both \(x_1\) and \(x_2\) begin in \(R\), but \(x_0\) leaves \(S\) before either leaves \(R\).

A python script that will produce movies for the dynamics for arbitrary \(0 < r \leq s < 1\) can be found at: \(\text{http://oak.cats.ohiou.edu/~rb301008/research.html}\).

### 2.4 Additional orbits

Besides orbits bifurcating with fixed points, based on numerics and on properties of the symbolic dynamics, additional orbits of \(F\) exist depending on parameters. Their existence domains do not coincide with those listed above.

* The most important orbits are the one-parameter family of period-3 neutral-stable orbits lying on the edges (and with code 1 \(\mapsto\) 1 \(\mapsto\) 11 \(\mapsto\) 1)

\[(0, x_2) \mapsto (1 - x_2, 1 - x_2) \mapsto (x_2, 1)\]

These orbits exist for arbitrary \(x_2 \in (1 - r + s, r - s)\) provided that \(\frac{1}{2} + s \leq r < 1 - \frac{5s}{3}\). They are stable with respect to transverse perturbations. The coordinates form 3 open intervals, each included in one the edges. Moreover, the interval boundaries respectively form a period-3 hyperbolic orbit (code 2 \(\mapsto\) 1 \(\mapsto\) 11 \(\mapsto\) 2) and a period-3 neutral-unstable orbit (code 1 \(\mapsto\) 4 \(\mapsto\) 11 \(\mapsto\) 1) which exist in the same parameter domains and which merge for \(r = \frac{1}{2} + s\). Orbits in the family correspond to 2 clusters solutions in the original system with one cluster composed of two clusters (and the two clusters being certainly isolated one from each other).

* Interestingly, the bifurcation at \(r = \frac{1}{2} + s\) generates two distinct periodic orbits with identical code (2 \(\mapsto\) 4 \(\mapsto\) 11 \(\mapsto\) 2). Both orbits are neutral-unstable and the first has coordinates

\[\left(\frac{3 - 6(r - s)}{4}, \frac{3 - 2(r - s)}{4}\right) \mapsto (r - s, \frac{3 - 2(r - s)}{4}) \mapsto (r - s, 2(r - s))\]
with the first point being in 2. It exists under the condition $\frac{1}{2} + \frac{s}{3} \leq r \leq \frac{1}{2} + s$.

The other solution is actually a one-parameter family of periodic orbits (which forms a segment and) whose component in 11 is $\left(\frac{5(s-r)+3s_2}{11}, x_2\right)$ where $x_2$ can be chosen arbitrary with the condition

$$\frac{3}{4}(1-x_2) \leq \min \left\{ \frac{3-6(r-s)}{5}, \frac{6r+5s-3}{7} \right\}$$

The family exists under the condition $\frac{1}{2} - \frac{5s}{6} \leq r \leq \frac{1}{2} + s$.

The bifurcations taking place at $r = \frac{1}{2} + \frac{s}{3}$ and $r = \frac{1}{2} - \frac{5s}{6}$ are unclear. The fact that the one-parameter family reaches the boundary with 5 in the former case suggests to investigate orbits with code 4 $\mapsto$ 11 $\mapsto$ 5. Surprisingly, the analysis concludes that such an orbit exits only if $r = \frac{1}{2} + \frac{s}{3}$, a value that is unrelated to the one-parameter family existence condition.

Two additional orbits have been found on the edge when $2s < r \leq \frac{1}{2} + \frac{s}{12}$. One is hyperbolic with code 2 $\mapsto$ 8 $\mapsto$ 11 $\mapsto$ 2 and coordinates

$$ (0, r - \frac{s}{2}) \mapsto (1 - r + \frac{s}{6}, 1 - r + \frac{s}{6}) \mapsto (r - \frac{s}{2}, 1) \mapsto (0, r - \frac{s}{2}). $$

The other one is neutral-unstable with code 2 $\mapsto$ 4 $\mapsto$ 11 $\mapsto$ 2 and coordinates

$$ (0, \frac{3+5(r-s)}{11}) \mapsto (1 - \frac{5+r-s}{11}, 1 - \frac{5+r-s}{11}) \mapsto (\frac{3+5(r-s)}{11}, 1) \mapsto (0, \frac{3+5(r-s)}{11}). $$

The two orbits merge for $r = \frac{1}{2} + \frac{s}{12}$ in a seemingly saddle-node bifurcation.

### 3 Discussion

In this note we have investigated only a portion of the possible parameter space $0 < s \leq r < 1$. It should be clear to the reader by this point that further investigations into other subsets of the parameters in this fashion are possible, but perhaps prohibitively time-consuming. We see that such studies are likely to also prove unprofitable, since numerical simulations show that no other types of dynamics occur other than those described here. One can download a python script that to investigate the dynamics for arbitrary $0 < r \leq s < 1$ at: [http://oak.cats.ohiou.edu/~rb301008/research.html](http://oak.cats.ohiou.edu/~rb301008/research.html).

The dynamics we have observed for these parameter sets closely resembles the dynamics of $k=2$ cluster systems analyzed in [1]. The $k=3$ fixed point of $F$ with positive feedback, like that for $k=2$ is either:

- isolated and locally unstable, or,
- contained in a neutrally stable set of period $k$ points.
In the later case the edges of the neutrally stable set are unstable. This case exists if either the three clusters are isolated from each other, or, if they interact in a non-essential way. In both cases the orbits of all other interior points are asymptotic to the boundary. Thus $k$ cyclic solutions for either $k = 2$ or $k = 3$ are practically unstable in the sense the arbitrarily small perturbations may lead to loss of stability and eventual merger of clusters. Since the single cluster solution (synchronization) is the only solution that is asymptotically stable, it would seem to be the most likely to be observed in application if the feedback is similar to the form we propose and is positive.

Acknowledgments:
B.F. thanks the Courant Institute (NYU) for hospitality. He was supported by CNRS and by the EU Marie Curie fellowship PIOF-GA-2009-235741. T.Y. and this work were supported by the NIH-NIGMS grant R01GM090207.

References

[1] Clustering in Cell Cycle Dynamics with General Response/Signaling Feedback, Todd R. Young, Bastien Fernandez, Richard Buckalew, Gregory Moses and Erik M. Boczko, under revision.