Instability of the Steady State Solution in Cell Cycle Population Structure Models with Feedback

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Abstract

We show that when cell-cell feedback is added to a model of the cell cycle for a large culture of cells, then instability of the steady state solution occurs in many cases. We show this in the context of a generic agent-based ODE model. If the feedback is positive, then instability of the steady state solution is proved for all parameter values except for a small set on the boundary of parameter space. For negative feedback we prove instability for nearly half the parameter space. We also show by example that instability in the other half may be proved on a case by case basis.

Keywords: yeast metabolic oscillations

1 Introduction

1.1 Background

Consider growing and dividing cells in a laboratory setting, such as a bioreactor. Let x denote some measure of progress of a cell through its cell cycle (such as cell volume), If the number of cells is large, then we may reasonably represent the state of the system by a density function $\phi(x,t)$ rather than by the collection of the states of all the cells, $\{x_i\}_{i=1}^n$. Bell and Andersen [(1967), (1968)] introduced and studied a Partial Differential Equation model of the time evolution of such density functions $\phi(x,t)$. One feature of many of these models is the existence of a "steady state" solution $\bar{\phi}(x,t) = \phi_0(x)$ (perhaps after

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normalization). In this context, while the state state density function is a constant in time the individual cells represented by the solution are progressing in the cycle.

Several authors studied variants of the PDE models ([Zeit (1977)], [Diekmann et al. (1984)], [Hannsgen and Tyson (1985)], [Hannsgen et al. (1985)], [Heijmans (1984)], [Heijmans (1985)], [Lasota and Mackey (1984)], [Tyson and Hannsgen (1985)], [Tyson and Hannsgen (1985)]) with assumptions that correspond to some randomness in the division times of cells, e.g. the volume at which a cell divides is governed by some probability density function, $d(x)$. All of these studies concluded that the stationary solution is asymptotically stable. Diekmann et al. [(1993a), (1993b)] proved similar results for models based on renewal equations.

In these studies, the models did not include any feedback between cells in the culture. Motivated by a phenomenon in yeast called Autonomous Oscillations (see e.g. [Murray et al. (2003), Robertson et al. (2008)]), we introduced Ordinary Differential Equations (ODE) models of cell cultures in which cells in some phase of the cell cycle may produce chemical agents that effect the cell cycle progress of cells in some other part [Boczko et al. (2010), Young et al. (2012)]. We observed that such models frequently exhibit stable synchronous or periodic clustered solutions and stability of synchronous or certain clustered solutions was proved in many cases [Young et al. (2012), Breitsch et al. 2015]. However, the discrete equivalent of the steady-state solution, which we call the *uniform* solution (see definition below), appears unstable in all simulations.

In this paper we prove that the uniform solution is unstable for a large set of parameter values in the ODE model with feedback. The proof relies on showing that the derivative of the Poincaré return map has an eigenvalue outside of the unit circle by studying a certain "partial return map." It proceeds in several cases that we explain after introducing the model.

1.2 Notation and the model

We study a dynamical model of the mitotic cell division cycle (CDC) for cultures of a large number of cells in which cells in one fixed region of the cycle S (Signaling) produce chemical agents that affect the growth and development rate of cells in another fixed region R (Responsive). Let the state of the i-th cell be denoted $c_i \in [0, 1) \equiv S^1$ and let its progression be governed by the equation:

$$\frac{dc_i}{dt} = \begin{cases} 1, & \text{if} \quad c_i \notin R \\ 1 + f(I), & \text{if} \quad c_i \in R, \end{cases} \qquad i = 1, ..., n, \tag{1.1}$$

where

$$I(c) \equiv \frac{\#\{i : c_i \in S\}}{n} \quad \text{(fraction of cells in the signaling region).} \tag{1.2}$$

The "response function" $f(I)$ in (1.1) should satisfy $f(0) = 0$ and be monotone, but may be non-linear, and either positive or negative. We suppose that $1 + f(I) > 0$ for all I

When a cell reaches 1 (division) two cells appear at 0. However, in this model the trajectories of the two cells will be identical, so we will only keep track of one of them. In other words, the number of cells is assumed to be fixed.

For definiteness, let R and S be regions on the circle ($[0, 1]$ where $1 \sim 0$), with $R = [r, 1)$ and $S = [0, s)$. R and S are adjacent at $1 \sim 0$. (One may also suppose that there is a gap between R and S [Gong et al. (2014a)].) We consider r and s as parameters and we assume $0 \leq s \leq r \leq 1$, i.e. the possible parameter values form a triangle.

In model (1.1), if two cells are initially synchronized in the cell cycle, they will remain so for all time. We will refer to subpopulations of synchronized cells as **cohorts**.

We reformulate (1.1) so that cohorts take the place of cells. Let k denote the number of cohorts and we suppose that each cohort contains n/k cells, so that they are identical in the model. Denote the position of the j-th cohort at time t by $x_j(t)$ for $j = 1, ..., k$. We will then study the dynamics of the cohorts; the equations governing the cohorts are similar to those governing individual cells,

$$\frac{dx_j}{dt} = \begin{cases} 1, & \text{if} \quad x_j \notin R \\ 1 + f(I), & \text{if} \quad x_j \in R, \end{cases} \qquad \text{for } j = 1, ..., k, \tag{1.3}$$

where I is the fraction of cohorts in S; $I = \#\{j : x_j \in S\}/k$. The variable I in this equation coincides with the fraction of cells, so f is the same as in (1.1).

We will focus on solutions of the form described in the following definition.

Definition 1.1 *Suppose that there exists a positive number d such that $x_j(d) = x_{j+1}(0)$ for $j = 1, ..., k-1$ and $x_k(d) = x_1(0)$ mod 1. We call $\{x_j\}$ a **k-cyclic solution**. We call a solution **uniform** if it is n-cyclic, i.e. each cohort consists of a single cell.*

The uniform solution (n-cyclic) is the finite cell equivalent of the steady state distribution in the PDE models. A topological argument shows that a k-cyclic solution exists for any k that is a divisor of n [Young et al. (2012)].

Theorem 1.2 ([Young et al. (2012)]) *For any monotone f and any $0 \leq s \leq r \leq 1$ and any k that divides n, the system (1.1) possesses a k-cyclic solution. In particular, a uniform solution ($k = n$) always exists.*

1.3 The map F and "events"

Since we assume that $1 + f(I) > 0$, the cells are moving with positive speed and so the set $\{x_1 = 0\}$ is a Poincaré section for the flow, with a well-defined Poincaré map P. It is useful to define a map $F : \{x_1 = 0\} \to \{x_k = 1\}$ as follows:

$$F(x_2, x_3, ..., x_k) = (x_1(t^*), x_2(t^*), ..., x_{k-1}(t^*)),$$

where t^* is the time required for $x_k(t)$ to reach 1. Note that, with an cyclic reordering of indices, F is a continuous map from the simplex $\{0 < x_2 < \ldots < x_k < 1\}$ into itself, that is, $F(x_2, \ldots, x_k) = (\bar{x}_2, \ldots, \bar{x}_k) \equiv (x_1(t^*), \ldots, x_{k-1}(t^*))$. It can be extended continuously to the boundary of the simplex [Young et al. (2012)]. Further,

- F^k is the Poincaré map, and,
- a fixed point of F is an initial condition on $\{x_1 = 0\}$ of a cyclic solution and vice versa.

Calculation of F hinges on the *order of events* – a cohort's progress through the cell cycle can be described in terms the solution reaching certain milestones, such as a cohort entering R. Cohorts progress through the cell cycle at rates specified by the equation (1.1). These rates remain constant until a cohort reaches s, r, or 1 which we label as events **s**, **r**, and **1** respectively.

Let σ denote the number of cohorts in S, ρ the number of cohorts in the complement of R. Thus at the beginning of a time interval on which the map F is applied the initial positions of the k cohorts will be:

$$0 = x_1 < \ldots < x_\sigma < s \leq x_{\sigma+1} < \ldots < x_\rho < r \leq x_{\rho+1} < \ldots < x_k < 1. \tag{1.4}$$

1.4 The cyclic solution, partitions of parameter space and stability

Given parameters (r, s) and an initial condition $\mathbf{x}$, the partial return map F runs time until event **1** occurs. Being a cyclic solution imposes restrictions upon the order of events.

Proposition 1.3 *[Breitsch et al. 2015] The sequence of events followed by the cyclic solution is either* **s**, **r**, **1**, *. . . or* **r**, **s**, **1**, *. . .*

This proposition and other results in [Breitsch et al. 2015] imply that for a given k, parameter space $0 \leq s \leq r \leq 1$ is subdivided in subtriangles that are characterized by the order of event of the k-cyclic solution. See Figure 1.

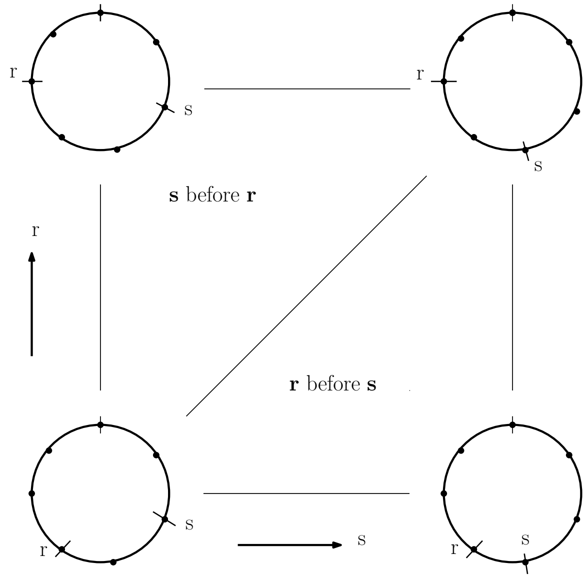

Figure 1: The order of events of a k-cyclic solution partitions $s-r$ parameter space into triangles. "Upper left" triangle correspond to event **s** occurring first while "lower right" triangle correspond to event **r** first.

Further, in [Breitsch et al. 2015] it was shown that for all parameters within a single order of events subtriangle, the derivative of the map F, DF, at a k cyclic solution is exactly the same. This allows for easy and accurate study of the stability of k cyclic solutions for k not too large. For instance, the stability for several values of k with positive feedback is calculated and illustrated in Figure 2. We completed these calculations for $k = 2$ up to $k = 100$ and observed that for positive feedback the k-cyclic solutions are never asymptotically stable for any $k \geq 2$ [Breitsch et al. 2015]. The sub-triangles that do not share an edge with the boundary are all unstable. We will prove this result in two parts, one proof for the "upper left" triangles (**sr1**) and another proof for the "lower right" triangles (**rs1**).

The stability of k cyclic solutions under negative feedback for $k = 2, \ldots, 13$ are shown in Figure 3. Note that the "upper left triangles" that don't intersect the boundary are all red, meaning that the k-cyclic solution is unstable. These sub triangles correspond to the order of events **sr1** and we will prove the instability for this case. For k prime all of the interior subtriangles are colored red, indicating unstable k-cyclic solutions.

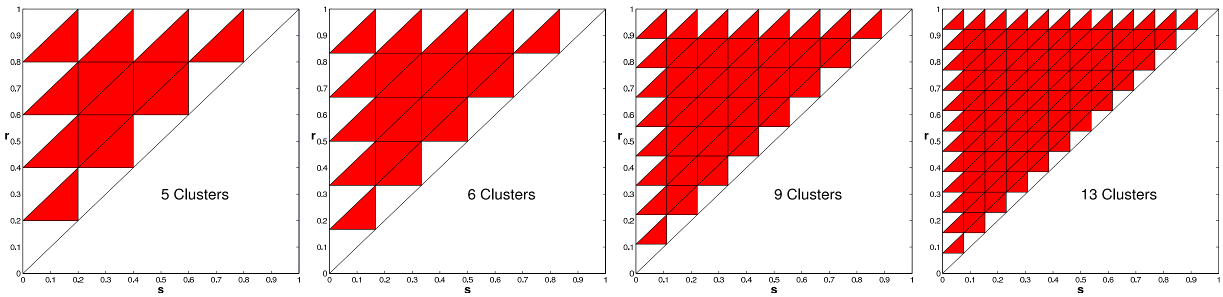

Figure 2: Red - Unstable; White - Neutral. Positive Feedback. Parameter regions of instability for k-cyclic clustered solutions under with $k = 5, 6, 9, 13$. The picture is similar for any $k \geq 2$. There are no regions of stability for the clustered solutions with positive feedback. We will prove instability of k cyclic solutions for parameter values in all of the red triangles. (Color figure online.)

1.5 Results

We will need to assume the conditions:

$$1 < \sigma < \rho < k. \tag{1.5}$$

This ensures that parameter values are not in a sub triangle that intersects the boundary of the parameter space $\{0 \leq s \leq r \leq 1\}$.

Theorem 1.4 *Suppose that the response function $f(I)$ is positive and increasing and that ϕ^t is a k-cyclic solution such that (1.5) holds, or, suppose that (1.5) does not hold but that the order of events of ϕ^t is* **rs1**. *Then ϕ^t is linearly unstable.*

By linearly unstable we mean that the derivative of the Poincaré map has an eigenvalue outside the unit disk. This implies that the cyclic solution is either a source or a saddle orbit.

Theorem 1.5 *Suppose that the response function $f(I)$ is negative and decreasing and that ϕ^t is a k-cyclic solution with order of events* **sr1** *and such that (1.5) holds. Then ϕ^t is linearly unstable.*

Proposition 1.6 *Suppose that the response function $f(I)$ is negative and decreasing and that ϕ^t is a k-cyclic solution with order of events* **rs1** *and such that (1.5) holds. Assume further that k is odd, while σ and ρ are even. Then ϕ^t is linearly unstable.*

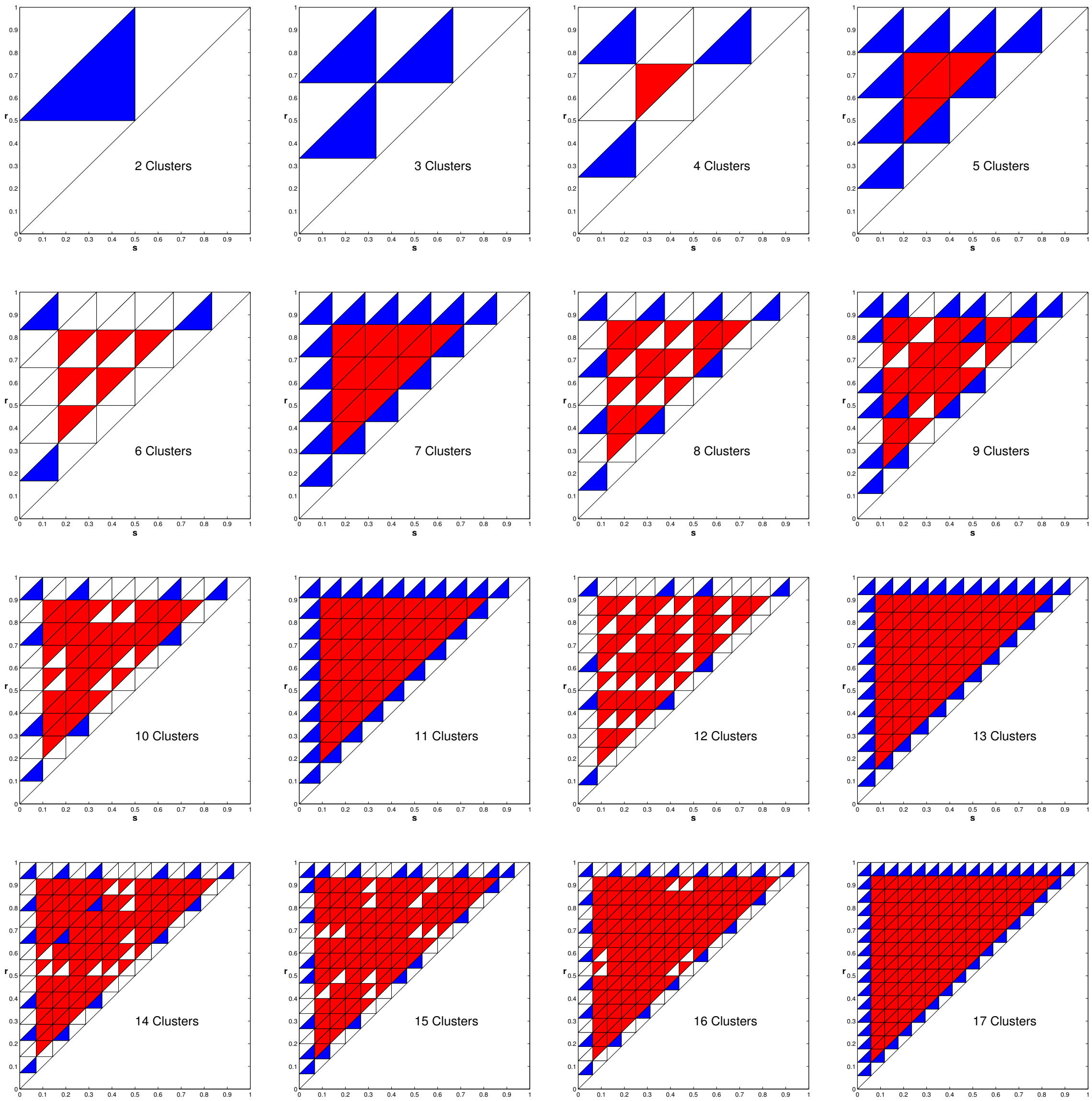

Figure 3: Stability of parameter regions for k-cyclic clustered solutions with negative feedback. Blue - Asymptotically Stable; Red - Unstable; White - Neutral. Reproduced from [Breitsch et al. 2015]. Note that the interior "upper left" (**sr1**) triangles are all red. We prove instability for these cases and for one special case with order of events **rs1** and small feedback. (Color figure online.)

2 Calculating F

2.1 Common features

We start with an initial condition on the Poincare section $\{x_1 = 0\}$. Assume that for the k-cyclic solution no two clusters have the same initial condition and do not coincide with either s or r. Thus, the initial condition satisfies (1.4) with strict inequalities. We also assume that, $s - x_\sigma \neq r - x_\rho$, so that events **s** and **r** do not occur simultaneously. Then in a small neighborhood of the k-cyclic solution, the solutions will follow the same order of event as the cyclic solution for the finite time period corresponding to one application of the F map.

For an initial condition in this small neighborhood let t^* denote the time required for one application of the map F, i.e. t^* is the minimum $t > 0$ such that:

$$x_k(t^*) = 1.$$

Note that clusters with indices i, $1 \le i \le \rho - 1$ will progress with rate 1 during the time period $0 < t < t^*$. Thus the exact solution for these indices is:

$$x_i(t) = x_i + t, \qquad 0 \le t \le t^*, \quad 1 \le i \le \rho - 1$$

and so

$$x_i(t^*) = x_i + t^*, \qquad 1 \le i \le \rho - 1.$$

Since $x_1(0) = 0$, $x_1(t^*) = t^*$.

2.2 Order of events sr1

Let $\beta_i = f(i/k)$.

In this case $s - x_\sigma < r - x_\rho$. For $\rho + 1 \le i \le k$ the clusters progresses with rate $1 + \beta_\sigma$ while $x_\sigma < s$ and with rate $1 + \beta_{\sigma-1}$ while $x_\sigma > s$. Thus

$$x_i(t) = x_i + (1 + \beta_\sigma)t, \qquad 0 \le t \le s - x_\sigma, \quad \rho + 1 \le i \le k,$$

and

$$x_i(t)|_{t=s-x_\sigma} = x_i + (1 + \beta_\sigma)(s - x_\sigma).$$

These clusters then progress with rate $1 + \beta_{\sigma-1}$ until t^*:

$$\begin{aligned} x_i(t) &= x_i + (1 + \beta_\sigma)(s - x_\sigma) + (1 + \beta_{\sigma-1})(t - s + x_\sigma) \\ &= x_i + (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) + (1 + \beta_{\sigma-1})t, \end{aligned}$$

for $s - x_\sigma \leq t \leq t^*$. For x_k we have:

$$x_k + (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) + (1 + \beta_{\sigma-1})t^* = 1$$

or

$$t^* = \frac{1}{1+\beta_{\sigma-1}} \left(1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma)\right). \tag{2.1}$$

Thus, for $\rho + 1 \leq i \leq k - 1$ we have:

$$\begin{aligned} x_i(t^*) &= x_i + (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) + 1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) \\ &= x_i + 1 - x_k. \end{aligned}$$

By assumption $x_k(t^*) = 1$.

Now consider $i = \rho$. The solution is $x_\rho(t) = x_\rho + t$ for $0 \leq t \leq r - x_\rho$ and (as expected from the definitions) $x_\rho(t)|_{t=r-x_\rho} = x_\rho + r - x_\rho = r$.

After x_ρ enters R at time $r - x_\rho$ it progresses with rate $1 + \beta_{\sigma-1}$:

$$x_\rho(t) = r + (1 + \beta_{\sigma-1})(t - r + x_\rho), \qquad r - \sigma_\rho \leq t \leq t^*.$$

Then we have:

$$\begin{aligned} x_\rho(t^*) &= r + (1 + \beta_{\sigma-1})(t^* - r + x_\rho) \\ &= r + 1 - x_k + (\beta_\sigma - \beta_{\sigma-1})(-s + x_\sigma) + (1 + \beta_{\sigma-1})(-r + x_\rho). \end{aligned}$$

Summarizing, for order of events **sr1**:

$$\begin{aligned} x_1(t^*) &= t^* = \frac{1}{1+\beta_{\sigma-1}} \left(1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma)\right) \\ x_i(t^*) &= x_i + \frac{1}{1+\beta_{\sigma-1}} \left(1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma)\right), \qquad 2 \leq i \leq \rho - 1, \\ x_\rho(t^*) &= r + 1 - x_k + (\beta_\sigma - \beta_{\sigma-1})(-s + x_\sigma) + (1 + \beta_{\sigma-1})(-r + x_\rho), \\ x_i(t^*) &= x_i + 1 - x_k, \qquad \rho + 1 \leq i \leq k - 1, \\ x_k(t^*) &= 1. \end{aligned} \tag{2.2}$$

2.3 Order of events rs1

In this case $s - x_\sigma > r - x_\rho$. First we note that the solutions for $1 \leq i \leq \rho - 1$ and $\rho + 1 \leq i \leq k$ are exactly the same are for the order **sr1**. Thus we only have to calculate $x_\rho(t)$. Trivially, we have that $x_\rho(t) = r$ at $t = r - x_\rho$.

During the time span $r - x_\rho \leq t \leq s - x_\sigma$, $x_\rho(t)$ follows the solution:

$$x_\rho(t) = r + (1 + \beta_\sigma)(t - r + x_\rho),$$

and so,

$$x_\rho(t)|_{t=s-x_\sigma} = r + (1+\beta_\sigma)(s - x_\sigma - r + x_\rho).$$

For $s - x_\sigma \le t \le t^*$, x_ρ progresses with rate $1 + \beta_{\sigma-1}$:

$$\begin{aligned} x_\rho(t) &= r + (1+\beta_\sigma)(s - x_\sigma - r + x_\rho) + (1+\beta_{\sigma-1})(t - s + x_\sigma) \\ &= r + (1+\beta_\sigma)(-r + x_\rho) + (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) + (1+\beta_{\sigma-1})t. \end{aligned}$$

At time $t = t^*$, (using t^* from equation (2.1)), we have

$$\begin{aligned} x_\rho(t^*) &= r + (1+\beta_\sigma)(-r + x_\rho) + (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) + 1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma) \\ &= r + (1+\beta_\sigma)(-r + x_\rho) + 1 - x_k. \end{aligned}$$

Therefore, for order of events **rs1**

$$\begin{aligned} x_1(t^*) &= t^* = \frac{1}{1+\beta_{\sigma-1}}\left(1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma)\right) \\ x_i(t^*) &= x_i + \frac{1}{1+\beta_{\sigma-1}}\left(1 - x_k - (\beta_\sigma - \beta_{\sigma-1})(s - x_\sigma)\right), \qquad 2 \le i \le \rho - 1, \\ x_\rho(t^*) &= r + (1+\beta_\sigma)(-r + x_\rho) + 1 - x_k, \\ x_i(t^*) &= x_i + 1 - x_k, \qquad \rho + 1 \le i \le k - 1, \\ x_k(t^*) &= 1. \end{aligned} \tag{2.3}$$

Boundary case: $\sigma = 1$:
In this case $x_\sigma = x_1 = 0$ and $\beta_{\sigma-1} = \beta_0 = 0$, which simplifies the above F map considerably:

$$\begin{aligned} x_1(t^*) &= t^* = 1 - x_k - \beta_1 s \\ x_i(t^*) &= x_i + 1 - x_k - \beta_1 s, \qquad 2 \le i \le \rho - 1, \\ x_\rho(t^*) &= r + (1+\beta_1)(x_\rho - r) + 1 - x_k, \\ x_i(t^*) &= x_i + 1 - x_k, \qquad \rho + 1 \le i \le k - 1, \\ x_k(t^*) &= 1. \end{aligned} \tag{2.4}$$

Boundary case: $\rho = k$:
If $\rho = k$ we have to recalculate the trajectory of $x_\rho = x_k$ and t^*. Trivially, we have that $x_k(t) = r$ for $t = r - x_k$.

During the time span $r - x_k \le t \le s - x_\sigma$, $x_k(t)$ follows the solution:

$$x_k(t) = r + (1+\beta_\sigma)(t - r + x_k),$$

and so,

$$x_k(t)|_{t=s-x_\sigma} = r + (1+\beta_\sigma)(s - x_\sigma - r + x_k).$$

Next during the period $s - x_\sigma \le t \le t^*$, $x_k(t)$ moves with rate $1 + \beta_{\sigma-1}$:

$$x_k(t) = r + (1+\beta_\sigma)(s - x_\sigma - r + x_k) + (1+\beta_{\sigma-1})(t - s + x_\sigma).$$

Thus,

$$x_k(t^*) = 1 = r + (1+\beta_\sigma)(s - x_\sigma - r + x_k) + (1+\beta_{\sigma-1})(t^* - s + x_\sigma),$$

and solving for t^* gives:

$$\begin{aligned} t^* &= -s - x_\sigma + \frac{1-r}{1+\beta_{\sigma-1}} + \frac{1+\beta_\sigma}{1+\beta_{\sigma-1}}(s - r + x_k - x_\sigma) \\ &= -(2+w)x_\sigma + (1+w)x_k + \text{constant terms} \end{aligned} \tag{2.5}$$

Then for all $i < k$ we have:

$$x_i(t^*) = x_i + t^*.$$

2.4 DF for the cases sr1 and rs1

Let

$$w = \frac{\beta_\sigma - \beta_{\sigma-1}}{1+\beta_{\sigma-1}} \quad \text{and} \quad v = \frac{1}{1+\beta_{\sigma-1}}.$$

First, for the order of events **sr1**, from (2.2):

$$DF_{\mathbf{sr1}} = \begin{array}{c} \\ 1 \\ \\ \\ \\ \\ \sigma \\ \\ \\ \\ \rho \\ \\ \\ \\ \end{array} \begin{array}{c} \begin{array}{ccccccccccccc} 1 & & & & \sigma-1 & & & & \rho-1 & & & & k-1 \end{array} \\ \left(\begin{array}{ccccccccccccc} 0 & 0 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 1 & 0 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 0 & 1 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ \vdots & \cdots & \ddots & \cdots & \vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots \\ 0 & 0 & \cdots & 1 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 0 & 0 & \cdots & 0 & 1+w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 0 & 0 & \cdots & 0 & w & 1 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ \vdots & \cdots & \cdots & \cdots & \vdots & \cdots & \ddots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & w & 0 & \cdots & 1 & 0 & 0 & \cdots & 0 & -v \\ 0 & 0 & \cdots & 0 & \beta_\sigma - \beta_{\sigma-1} & 0 & \cdots & 0 & v^{-1} & 0 & \cdots & 0 & -1 \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 1 & \cdots & 0 & -1 \\ \vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \ddots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 1 & -1 \end{array}\right) \end{array}. \tag{2.6}$$

There are 1's on the sub-diagonal except for the σ-th row $(1+w)$ and the ρ-th row $(v^{-1} = 1 + \beta_{\sigma-1})$. Only two columns, the $(\sigma-1)$-th and the $(k-1)$-th, have entries off the sub diagonal. The terms in the last column change to -1's at the ρ-th row. The $\beta_\sigma - \beta_{\sigma-1}$ term is in the $(\sigma-1)$-th column and the ρ-st row. Above this, the entries are w's and below it zeros.

This formula is valid for all k-cyclic solutions in the same event triangle i.e. for a fixed triplet of integers (ρ, σ, k) and the order of events **s** before **r**. Also note that there are some simpler cases, such as when $\sigma = 1$ or $\rho = k$, that have been investigated elsewhere.

Next for the order of events **rs1**. It follows from (2.3) that

$$DF_{\mathbf{rs1}} = \begin{array}{c} \\ 1 \\ \\ \\ \\ \\ \sigma \\ \\ \\ \\ \rho \\ \\ \\ \\ \end{array} \begin{array}{c} \begin{array}{cccccccccccccc} 1 & & & & \sigma-1 & & & & \rho-1 & & & & k-1 \end{array} \\ \left(\begin{array}{cccccccccccccc}
0 & 0 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\
1 & 0 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\
0 & 1 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\
\vdots & \cdots & \ddots & \cdots & \vdots & \cdots & \cdots & . & \cdots & \cdots & \cdots & \cdots & \vdots \\
0 & 0 & \cdots & 1 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\
0 & 0 & \cdots & 0 & 1+w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\
0 & 0 & \cdots & 0 & w & 1 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\
\vdots & \cdots & \cdots & \cdots & \vdots & \cdots & \ddots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots \\
0 & 0 & \cdots & 0 & w & 0 & \cdots & 1 & 0 & 0 & \cdots & 0 & -v \\
0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 1+\beta_\sigma & 0 & \cdots & 0 & -1 \\
0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 1 & \cdots & 0 & -1 \\
\vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & . & \cdots & \cdots & \ddots & \cdots & \vdots \\
0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 1 & -1
\end{array}\right) \end{array}. \tag{2.7}$$

There are 1's down the sub-diagonal except for the σ-th row $(1 + w)$ and the ρ-th row $(1 + \beta_\sigma)$. The terms in the last columns changes to -1's at the ρ-th row. The three columns with terms other than 0 and 1 are the $(\sigma-1)$-th, the $(\rho-1)$-th, and the $(k-1)$-th. The w terms in the $\sigma - 1$-th column change to zeros at the ρ-st row. All other columns have exactly one 1 entry and $k - 2$ zeros.

Note that in both cases $tr(DF) = -1 + w$.

Boundary case: $\sigma = 1$
In this case we have:

$$DF_{\mathbf{rs1}} = \begin{array}{c} \\ 1 \\ \\ \\ \\ \\ \rho \\ \\ \\ \\ \end{array} \begin{array}{c} \begin{array}{ccccccccc} 1 & & & & \rho-1 & & & & k-1 \end{array} \\ \left(\begin{array}{ccccccccc}
0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -1 \\
1 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -1 \\
0 & 1 & \cdots & 0 & 0 & 0 & \cdots & 0 & -1 \\
\vdots & \cdots & \ddots & \cdots & \vdots & \cdots & \cdots & \cdots & \vdots \\
0 & 0 & \cdots & 1 & 0 & 0 & \cdots & 0 & -1 \\
0 & 0 & \cdots & 0 & 1+\beta_\sigma & 0 & \cdots & 0 & -1 \\
0 & 0 & \cdots & 0 & 0 & 1 & \cdots & 0 & -1 \\
\vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \ddots & \cdots & \vdots \\
0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 1 & -1
\end{array}\right) \end{array}. \tag{2.8}$$

Boundary case: $\rho = k$

$$
DF_{\mathbf{rs1}} = \begin{array}{cc} & \begin{array}{ccccccccc} 1 & & & & \sigma-1 & & & & k-1 \end{array} \\ \begin{array}{c} 1 \\ \\ \\ \\ \\ \sigma \\ \\ \\ \\ \end{array} & \begin{pmatrix} 0 & 0 & \cdots & 0 & -2-w & 0 & \cdots & 0 & 1+w \\ 1 & 0 & \cdots & 0 & -2-w & 0 & \cdots & 0 & 1+w \\ 0 & 1 & \cdots & 0 & -2-w & 0 & \cdots & 0 & 1+w \\ \vdots & \cdots & \ddots & \cdots & \vdots & \cdots & \cdots & \cdots & \vdots \\ 0 & 0 & \cdots & 1 & -2-w & 0 & \cdots & 0 & 1+w \\ 0 & 0 & \cdots & 0 & -1-w & 0 & \cdots & 0 & 1+w \\ 0 & 0 & \cdots & 0 & -2-w & 1 & \cdots & 0 & 1+w \\ \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \ddots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & -2-w & 0 & \cdots & 1 & 1+w \end{pmatrix} \end{array}. \tag{2.9}
$$

Determinant of DF

Case sr1: After $k-2$ row swamps, the matrix $DF_{\mathbf{sr1}}$ is transformed to:

$$
A = \begin{array}{cc} & \begin{array}{ccccccccccccc} 1 & & & & \sigma-1 & & & & \rho-1 & & & & k-1 \end{array} \\ \begin{array}{c} 1 \\ \\ \\ \\ \sigma-1 \\ \\ \\ \\ \rho-1 \\ \\ \\ \\ \\ \end{array} & \begin{pmatrix} 1 & 0 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 0 & 1 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ \vdots & \cdots & \ddots & \cdots & \vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots \\ 0 & 0 & \cdots & 1 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 0 & 0 & \cdots & 0 & 1+w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ 0 & 0 & \cdots & 0 & w & 1 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \\ \vdots & \cdots & \cdots & \cdots & \vdots & \cdots & \ddots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & w & 0 & \cdots & 1 & 0 & 0 & \cdots & 0 & -v \\ 0 & 0 & \cdots & 0 & \beta_\sigma-\beta_{\sigma-1} & 0 & \cdots & 0 & v^{-1} & 0 & \cdots & 0 & -1 \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 1 & \cdots & 0 & -1 \\ \vdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \ddots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 1 & -1 \\ 0 & 0 & \cdots & 0 & w & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 & -v \end{pmatrix} \end{array}. \tag{2.10}
$$

Note that $det(DF_{\mathbf{sr1}}) = (-1)^{k-2}det(A)$. Below the diagonal, A has non-zero entries only in the $(\sigma-1)$-th column. We can then do Gaussian Elimination, using only multiples of the $(\sigma-1)$-th row, to put A into an upper triangular form U in which the diagonal elements are unchanged, except the new lower right corner entry is given by:

$$
U_{k-1,k-1} = -v + \frac{w}{1+w}v = \frac{-1}{1+\beta_\sigma}.
$$

We then have that

$$
det(DF_{\mathbf{sr1}}) = (-1)^{k-1}(1+w)\frac{1+\beta_{\sigma-1}}{1+\beta_\sigma} = (-1)^{k-1}.
$$

Case rs1:

By a similar calculation we obtain

$$det(DF_{\mathbf{rs1}}) = (-1)^{k-1}(1+w) = (-1)^{k-1}\frac{1+\beta_\sigma}{1+\beta_{\sigma-1}}.$$

For the boundary case $\sigma = 1$ it is easy to see that the determinant of $DF_{\mathbf{rs1}}$ is simply $(-1)^{k-1}(1+\beta_1)$.

If we have $\rho = k$, the computation is a bit more complicated, but we obtain that the determinant of $DF_{\mathbf{rs1}}$ is $(-1)^{k-1}(1+w)$.

2.5 Characteristic Polynomials

Lemma 2.1 *The characteristic equation for $DF_{\mathbf{sr1}}$ at a k-cyclic solution under the conditions $1 < \sigma < \rho < k$ is*

$$\lambda^{k-1} + \ldots + \lambda + 1 = w\lambda^{\rho-\sigma+1}(\lambda^{\sigma-2} + \ldots + \lambda + 1)(\lambda^{k-\rho-1} + \ldots + \lambda + 1). \tag{2.11}$$

Proof: Note from $det(DF) = \pm 1$ that 0 cannot be an eigenvalue. Suppose that $\bar{y} = (y_1, y_2, \ldots, y_{k-1})$ is an eigenvector of $DF_{\mathbf{sr1}}$ and λ is the corresponding eigenvalue. Then

$$\begin{aligned}
wy_{\sigma-1} - vy_{k-1} &= \lambda y_1 \\
y_1 + wy_{\sigma-1} - vy_{k-1} &= \lambda y_2 \\
y_2 + wy_{\sigma-1} - vy_{k-1} &= \lambda y_3 \\
\vdots \quad &= \quad \vdots \\
y_{\sigma-1} + wy_{\sigma-1} - vy_{k-1} &= \lambda y_\sigma \\
\vdots \quad &= \quad \vdots \\
y_{\rho-2} + wy_{\sigma-1} - vy_{k-1} &= \lambda y_{\rho-1} \\
y_{\rho-1} + wy_{\sigma-1} - vy_{k-1} &= \lambda v y_\rho \\
y_\rho - y_{k-1} &= \lambda y_{\rho+1} \\
y_{\rho+1} - y_{k-1} &= \lambda y_{\rho+2} \\
\vdots \quad &= \quad \vdots \\
y_{k-2} - y_{k-1} &= \lambda y_{k-1}
\end{aligned} \tag{2.12}$$

Note that the index of y on the r.h.s of each equation corresponds to the index of the row in the matrix equation. We have multiplied row ρ by v to obtain the form above. The term $wy_{\sigma-1} - vy_{k-1}$ appears in all the equations indexed from 1 to ρ. Noting row 1 is:

$$wy_{\sigma-1} - vy_{k-1} = \lambda y_1, \tag{2.13}$$

if we substitute λy_1 for $wy_{\sigma-1} - vy_{k-1}$ in rows 2 to ρ then this subset of equations becomes:

$$\begin{aligned} y_1 + \lambda y_1 &= \lambda y_2 \\ y_2 + \lambda y_1 &= \lambda y_3 \\ \vdots &= \vdots \\ y_{\sigma-1} + \lambda y_1 &= \lambda y_\sigma \\ \vdots &= \vdots \\ y_{\rho-2} + \lambda y_1 &= \lambda y_{\rho-1} \\ y_{\rho-1} + \lambda y_1 &= \lambda v y_\rho \end{aligned} \tag{2.14}$$

Rows 2 through $\rho - 1$ may be solved recursively in terms of y_1:

$$y_i = \frac{\lambda^{i-1} + \lambda^{i-2} + \cdots + \lambda + 1}{\lambda^{i-1}} y_1, \qquad 2 \leq i \leq \rho - 1. \tag{2.15}$$

Of particular interest is the $\sigma - 1$ row:

$$y_{\sigma-1} = \frac{\lambda^{\sigma-2} + \cdots + \lambda + 1}{\lambda^{\sigma-2}} y_1. \tag{2.16}$$

Given the expression for $y_{\rho-1}$ from (2.15), the row ρ can be solved for y_ρ to give

$$y_\rho = (1 + \beta_{\sigma-1}) \frac{\lambda^{\rho-1} + \lambda^{\rho-2} + \cdots + \lambda + 1}{\lambda^{\rho-1}} y_1. \tag{2.17}$$

Next we see that, similarly, rows $\rho + 1$ through $k - 1$ can be solved recursively in terms of y_{k-1}, namely:

$$y_{k-1-i} = (\lambda^i + \lambda^{i-1} + \ldots + \lambda + 1) y_{k-1}. \tag{2.18}$$

Noting that $\rho = k - 1 - (k - \rho - 1)$ we obtain:

$$y_\rho = (\lambda^{k-\rho-1} + \ldots + \lambda + 1) y_{k-1}. \tag{2.19}$$

Now combining equations (2.13) and (2.16) we obtain:

$$v y_{k-1} = \left(w \frac{\lambda^{\sigma-2} + \cdots + \lambda + 1}{\lambda^{\sigma-2}} - \lambda \right) y_1. \tag{2.20}$$

Combining (2.17) and (2.19) yields:

$$\lambda^{\rho-1}(\lambda^{k-\rho-1} + \ldots + \lambda + 1) y_{k-1} = (1 + \beta_{\sigma-1})(\lambda^{\rho-1} + \lambda^{\rho-2} + \cdots + \lambda + 1) y_1. \tag{2.21}$$

Next, substituting (2.20) into (2.21) and multiplying by v leads to:

$$\lambda^{\rho-1}(\lambda^{k-\rho-1} + \ldots + \lambda + 1) \left(w \frac{\lambda^{\sigma-2} + \cdots + \lambda + 1}{\lambda^{\sigma-2}} - \lambda \right) y_1 = (\lambda^{\rho-1} + \lambda^{\rho-2} + \cdots + \lambda + 1) y_1.$$

We can solve this to obtain the equation in the theorem.

It is clear from the above equations that if $y_1 = 0$, then $\bar{y} = 0$. Also, if λ satisfies (2.11), then $y_1 \neq 0$ can be chosen arbitrarily and this choice will determine an eigenvector $\bar{y}$. Therefore λ is an eigenvalue if and only if it satisfies equation (2.11). It follows that if the roots of (2.11) are distinct, then it must be exactly the characteristic polynomial of $DF_{\mathbf{sr1}}$. More generally, the algebraic manipulations used to derive the polynomial were equivalent to Gaussian Elimination. Repeating those steps in matrix format show that this is indeed the characteristic polynomial. □

Lemma 2.2 *For $1 < \sigma < \rho < k$, the characteristic equation of $DF_{\boldsymbol{rs1}}$ at a k-cyclic solution is:*

$$\lambda^{k-1} + \ldots + \lambda + 1 = w\left[\lambda^{\rho-\sigma}(\lambda^{k-\rho} + \ldots + 1)(\lambda^{\sigma-2} + \ldots + 1) - (\lambda^{\rho-2} + \ldots + 1)\right]. \quad (2.22)$$

Proof: Note that the equations for this case are the same as for case **sr1**, except for the ρ-th row. In particular, equations (2.13), (2.15) and (2.16) still hold, as do (2.17), and (2.19).

In this case, row ρ is:

$$(1 + \beta_\sigma)y_{\rho-1} - y_{k-1} = \lambda y_\rho,$$

and so, substituting (2.17), we obtain:

$$(1 + \beta_\sigma)\frac{\lambda^{\rho-2} + \ldots + 1}{\lambda^{\rho-2}} y_1 - y_{k-1} = \lambda(\lambda^{k-\rho-1} + \ldots + \lambda + 1)y_{k-1}.$$

or

$$(1 + \beta_\sigma)\frac{\lambda^{\rho-2} + \ldots + 1}{\lambda^{\rho-2}} y_1 = (\lambda^{k-\rho} + \ldots + \lambda + 1)y_{k-1} \quad (2.23)$$

Combining (2.23 with (2.20)

$$v(1 + \beta_\sigma)\frac{\lambda^{\rho-2} + \ldots + 1}{\lambda^{\rho-2}} y_1 = (\lambda^{k-\rho} + \ldots + \lambda + 1)\left(w\frac{\lambda^{\sigma-2} + \cdots + \lambda + 1}{\lambda^{\sigma-1}} - \lambda\right) y_1.$$

Clearly if $y_1 = 0$ then $\bar{y} = 0$. Rearranging this equation then produces the result. □

3 Implications for the stability of k-cyclic solutions

3.1 Case rs1 and positive feedback

Since $det(DF_{\mathbf{rs1}}) = (-1)^{k-1}(1 + w) = (-1)^{k-1}\frac{1+\beta_\sigma}{1+\beta_{\sigma-1}}$, if the response function is positive and monotone increasing, so that $0 < \beta_{\sigma-1} < \beta_\sigma$,, i.e. $w > 0$ then we have that

$$|det(DF_{\mathbf{rs1}})| > 1,$$

including both boundary cases $\sigma = 1$ and $\rho = k$. This implies that at least one of the eigenvalues of $DF_{\mathbf{rs1}}$ is outside of the unit circle.

Proposition 3.1 *Suppose that the response function is positive and increasing and that ϕ^t is a k-cyclic solution with order of events* **rs1**. *Then ϕ^t is linearly unstable.*

This result appeared in [Moses (2015)].

3.2 Case sr1

Proposition 3.2 *Suppose that the response function is monotone increasing or decreasing and $1 < \sigma < \rho < k$. If ϕ^t is a k-cyclic solution with order of events* **sr1** *then ϕ^t is linearly unstable.*

This theorem is an improved version of a result in [Moses (2015)].

We will employ the following lemma, which is part of a classical theorem of Cohn [(1922)].

Lemma 3.3 *Let $p(z) = \sum_{n=0}^{d} a_n z^n$ be a complex polynomial such that all its roots are on the unit circle. Then there exists $c \in \mathbb{C}$ such that $|c| = 1$ and*

$$p(z) = cz^d \overline{p}(1/z),$$

where $\overline{p}(z) = \sum_{n=0}^{d} \overline{a_n} z^n$.

We provide a proof for the convenience of the reader. Proof: Let z_i, $|z_i| = 1$, for $i = 1, \ldots, d$, be the roots of polynomial p. Thus,

$$p(z) = a_d \prod_{i=1}^{d}(z - z_i) = \left(\prod_{i=1}^{d} z_i\right) a_d \prod_{i=1}^{d}\left(\frac{z}{z_i} - 1\right) = \left(\prod_{i=1}^{d} z_i\right) z^d a_d \prod_{i=1}^{d}\left(\frac{1}{z_i} - \frac{1}{z}\right)$$
$$= \left(\prod_{i=1}^{d} z_i\right) z^d \frac{a_d}{\overline{a_d}} \overline{a_d} \prod_{i=1}^{d}\left(\overline{z_i} - \frac{1}{z}\right) = \frac{a_d}{\overline{a_d}} \left(\prod_{i=1}^{d} z_i\right) z^d \overline{p}(1/z).$$

By choosing $c = \frac{a_d}{\overline{a_d}} \left(\prod_{i=1}^{d} z_i\right)$ the statement follows. □

Proof of Proposition 3.2: For either positive or negative feedback we have $|\det DF_{\mathbf{sr1}}| = 1$. This implies that either all of the eigenvalues of $DF_{\mathbf{sr1}}$ have modulus 1 or the fixed point of F is a saddle.

Let us argue by contradiction, that is, suppose that all of the roots of the equation (2.11) are on the unit circle. Let

$$p(\lambda) = \lambda^{k-1} + \ldots + \lambda + 1 - w\lambda^{\rho-\sigma+1}(\lambda^{\sigma-2} + \ldots + \lambda + 1)(\lambda^{k-\rho-1} + \ldots + \lambda + 1).$$

Then by Lemma 3.3, there exists $c \in \mathbb{C}$ with $|c| = 1$ such that $p(\lambda) = c\lambda^{k-1}\overline{p}(1/\lambda)$. But p has real coefficients, thus, $\overline{p} = p$. Therefore, $c \in \mathbb{R}$, i.e. $c = \pm 1$. Simple calculations show that

$$\lambda^{k-1}p(1/\lambda) = \lambda^{k-1} + \cdots + 1 - w\lambda(\lambda^{\sigma-2} + \cdots + 1)(\lambda^{k-\rho-1} + \cdots + 1).$$

By Lemma 3.3, the $k-1$th and $k-2$th coefficients of the polynomials $p(\lambda)$ and $c\lambda^{k-1}p(1/\lambda)$ must be equal, i.e. $c = 1$ and $1 - w = c$, which is a contradiction for $w \neq 0$. □

Taken together Propositions 3.1 and 3.2 imply Theorem 1.4 and Theorem 1.5.

3.3 Order of events rs1 and negative feedback

Calculations with negative feedback show that there are exceptional cases, i.e. triangles in the interior with neutral stability and even asymptotic stability with the order of events **rs1** (see Figure 3). All even k have exceptional triangles, even though these become smaller and more regular as k gets large. A few odd k, namely 9 and 15, also have exceptional sub triangles. Because of these cases, we cannot expect a general proof of instability for negative feedback and order of events **rs1**.

In this section we show in a special case that a small negative feedback still implies linear instability

Proposition 3.4 *Let us assume that $k > 1$ is odd and $\sigma < \rho$ are both even. Then there exists $\delta = \delta(k, \rho, \sigma) > 0$ such that*

$$-\delta < w = \frac{\beta_\sigma - \beta_{\sigma-1}}{1 + \beta_{\sigma-1}} < 0$$

then the k-cyclic solution with order of events **rs1** *is linearly unstable.*

First, consider the following which is consequence of trigonometric identities.

Lemma 3.5 *If $|\alpha - \beta| \leq \pi$ then*

$$e^{i\alpha} + e^{i\beta} = 2\cos\left(\frac{\alpha - \beta}{2}\right) e^{i\frac{\alpha+\beta}{2}}.$$

In particular, the argument of $e^{i\alpha} + e^{i\beta}$ is $\frac{\alpha+\beta}{2}$.

Proof of Proposition 3.4: It is easy to see that if $k > 1$ is odd then $\lambda_0 = e^{i\pi\frac{k-1}{k}}$ is root of the equation with $w = 0$, i.e. $\lambda^{k-1} + \ldots + \lambda + 1 = 0$. Since the roots are distinct, there exists (by the Implicit Function Theorem) a $\delta' = \delta'(k,\rho,\sigma) > 0$ and a smooth complex valued function $w \mapsto \lambda_0(w)$ such that

$$(\lambda_0(w))^{k-1} + \ldots + \lambda_0(w) + 1 =$$
$$w\left[(\lambda_0(w))^{\rho-\sigma}((\lambda_0(w))^{k-\rho} + \ldots + 1)((\lambda_0(w))^{\sigma-2} + \ldots + 1) - ((\lambda_0(w))^{\rho-2} + \ldots + 1)\right],$$

for every $w \in (-\delta', \delta')$ and $\lambda_0(0) = e^{i\pi\frac{k-1}{k}}$.

Thus, to prove the statement of the proposition, it is sufficient to show that the argument of $\frac{d\lambda_0}{dw}\Big|_{w=0}$ is contained in the interval $[0, \frac{k-2}{2k}\pi)$. Indeed, if the derivative satisfies this condition, then for small negative w, $\lambda_0(w) = e^{i\pi\frac{k-1}{k}} + w \cdot \frac{d\lambda_0}{dw}\Big|_{w=0} + o(w)$ is outside of the unit disc.

Consider

$$\frac{d\lambda_0}{dw}\Big|_{w=0} = \frac{\lambda^{\rho-\sigma}(\lambda^{k-\rho} + \ldots + 1)(\lambda^{\sigma-2} + \ldots + 1) - (\lambda^{\rho-2} + \ldots + 1)}{\frac{\partial}{\partial\lambda}(\lambda^{k-1} + \ldots + \lambda + 1)},$$

and

$$\frac{\partial}{\partial\lambda}(\lambda^{k-1} + \ldots + \lambda + 1) = \frac{(k-1)\lambda^k - k\lambda^{k-1} + 1}{(1-\lambda)^2}.$$

For $k > 1$ odd,

$$\frac{\partial}{\partial\lambda}(\lambda^{k-1} + \ldots + \lambda + 1)\Big|_{\lambda = e^{i\pi\frac{k-1}{k}}} = \frac{(k-1) - ke^{i\pi\frac{(k-1)^2}{k}} + 1}{(1 - e^{i\pi\frac{k-1}{k}})^2} = \frac{k(1 + e^{i\pi/k})}{(1 + e^{-i\pi/k})^2}.$$

The numerator above can also be simplified:

$$N(\lambda) = \lambda^{\rho-\sigma}(\lambda^{k-\rho} + \ldots + 1)(\lambda^{\sigma-2} + \ldots + 1) - (\lambda^{\rho-2} + \ldots + 1) = \frac{\lambda^k - \lambda^{k-\sigma+1} + \lambda^{\rho-\sigma} - \lambda^\rho + \lambda - 1}{(1-\lambda)^2}.$$

Then

$$\begin{aligned} N(e^{i\pi\frac{k-1}{k}}) &= \frac{e^{i\pi\frac{k-1}{k}k} - e^{i\pi\frac{k-1}{k}(k-\sigma+1)} + e^{i\pi\frac{k-1}{k}(\rho-\sigma)} - e^{i\pi\frac{k-1}{k}\rho} + e^{i\pi\frac{k-1}{k}} - 1}{(1 + e^{-i\pi/k})^2} \\ &= \frac{1 + e^{i\pi\frac{\sigma-1}{k}} + e^{i\pi\frac{\sigma-\rho}{k}} - e^{-i\pi\frac{\rho}{k}} - e^{-i\pi/k} - 1}{(1 + e^{-i\pi/k})^2} \\ &= \frac{(e^{-\frac{i\pi}{k}} + e^{-\frac{i\pi\rho}{k}})(e^{\frac{i\pi\sigma}{k}} - 1)}{(1 + e^{-i\pi/k})^2}. \end{aligned} \tag{3.1}$$

Using Lemma 3.5, we get

$$\begin{aligned} \frac{d\lambda_0}{dw}\Big|_{w=0} &= \frac{(e^{-\frac{i\pi}{k}} + e^{-\frac{i\pi\rho}{k}})(e^{\frac{i\pi\sigma}{k}} - 1)}{k(1 + e^{\frac{i\pi}{k}})} = \frac{2\cos\left(\frac{\rho-1}{2k}\pi\right)\cos\left(\frac{k-\sigma}{2k}\pi\right)}{k\left(\cos\left(\frac{1}{2k}\pi\right)\right)} \cdot \frac{e^{i\pi\frac{4k-\rho-1}{2k}}e^{i\pi\frac{\sigma+k}{2k}}}{e^{i\pi\frac{1}{2k}}} \\ &= \frac{2\cos\left(\frac{\rho-1}{2k}\pi\right)\cos\left(\frac{k-\sigma}{2k}\pi\right)}{k\left(\cos\left(\frac{1}{2k}\pi\right)\right)} e^{i\pi\frac{\sigma-\rho+k-2}{2k}}. \end{aligned}$$

Since $1 < k$, $2 \leq \sigma < \rho \leq k-1$ and $\rho - \sigma \geq 2$, we have

$$0 < \frac{1}{2k}\pi \leq \frac{k-\rho}{2k}\pi \leq \frac{k-\rho+\sigma-2}{2k}\pi \leq \frac{k-4}{2k}\pi < \frac{k-2}{2k}\pi,$$

which proves the result. □

4 Rate of instability

For k large we can show that σ/k is comparable to s (an adjustment due the feedback is necessary):

$$\frac{\sigma}{k} \approx s\frac{1+f(\frac{\sigma}{k})}{1+rf(\frac{\sigma}{k})}$$

In the case **sr1** and positive feedback we have that at least one eigenvalue has modulus at least $1+w$. Now

$$\beta_\sigma - \beta_{\sigma-1} = f(\frac{\sigma}{k}) - f(\frac{\sigma-1}{k}) \approx \frac{1}{k}f'(\frac{\sigma}{k}).$$

Thus, the spectral radius of DF is at least:

$$1 + \frac{1}{k}\frac{f'(\frac{\sigma}{k})}{1+\beta_{\sigma-1}}.$$

Thus we can say that the spectral radius of DF is of the order of $O(1+\frac{C}{k})$ for k large, where $C = f'(\frac{\sigma}{k})/(1+f(\frac{\sigma}{k})) > 0$. This give the impression of a weak instability. However, consider that $DP = DF^k$, so the spectral radius of DP is at least:

$$\left(1+\frac{C}{k}\right)^k \approx e^C.$$

Thus the rate of instability of the uniform solution in the flow is proportional to $f'(\frac{\sigma}{k})$.

In the case of Proposition 3.4 we see that at least one eigenvalue has modulus approximately

$$1 + \frac{C'w}{k},$$

and so a similar rate of instability estimate for the Poincaré map holds with rate proportional to w when k is large.

For the case **rs1** where instability was proved using Cohn's theorem (either positive or negative feedback), we do not readily have such an estimate.

5 Discussion

We have proven instability of k-cyclic solutions, including the uniform solution ($k = n$), for large sets of parameter values (s, r) in the interior of the parameter triangle. Specifically, we have proven instability when the feedback is positive in all possible cases. For negative feedback we have proven instability for all interior triangles with order of events **sr1**.

In the remaining case of negative feedback and order of events **rs1** we have proven instability in the sub-case of k odd while σ and ρ are even. We believe that this method of proof could be used for other sub-cases by considering other roots of the characteristic equation with $w = 0$ and finding combinations of k, σ, ρ that force the argument of $d\lambda/dw$ to be within the (large) set of angles that would make $\lambda(w)$ be outside the unit circle for small negative w. Since calculations show exceptional triangles for both k even and k odd, we cannot predict whether pursuing this line of proof would be exhaustive.

The results here taken together with the classical results discussed in the introduction suggest that in real systems with a feedback mechanism, there is competition between the phenomena of coherence and dispersion. Dispersion due to internal and external noise sources tends to stabilize the steady state, while feedback tends to destabilize the steady state while stabilizing either synchronous or clustered solutions (with k small). Gong et al. [(2014b)] using yeast autonomous oscillation data and simulations with biologically relevant noise, concluded that a relatively large feedback, on the order of 30% slow down for negative feedback, was necessary to destabilize the uniform solution and produce coherent clustering as seen in the experiments.

Proving instability of the steady state solution in PDE or renewal equation models with feedback would be an interesting and challenging problem. Because the steady state is really a periodic solution (cells are moving around the circle and perturbations from the steady state distribution will do the same), to determine stability one must study the Poincaré map or the equivalent Floquet theory along this solution. Thus, the problem is non-local in both space (x) and time.

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