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Discontinuity-induced bifurcation cascades in flows and maps with application to models of the yeast cell cycle

Mike R. Jeffrey [a], Harry Dankowicz [b,*]

[a] Department of Engineering Mathematics, University of Bristol, England, United Kingdom
[b] Department of Mechanical Science and Engineering, University of Illinois at Urbana-Champaign, USA

HIGHLIGHTS

- We investigate bifurcation cascades in models of the eukaryotic cell cycle.
- We develop a general theory for classes of period-adding cascades in piecewise-defined maps with gaps.
- The theory predicts characteristic scalings of bifurcation values that agree with numerical observations.
- We uncover global saddle–node bifurcations in piecewise-defined maps and piecewise-smooth hybrid dynamical systems.

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ABSTRACT

This paper applies methods of numerical continuation analysis to document characteristic bifurcation cascades of limit cycles in piecewise-smooth, hybrid-dynamical-system models of the eukaryotic cell cycle, and associated period-adding cascades in piecewise-defined maps with gaps. A general theory is formulated for the occurrence of such cascades, for example given the existence of a period-two orbit with one point on the system discontinuity and with appropriate constraints on the forward trajectory for nearby initial conditions. In this case, it is found that the bifurcation cascade for nearby parameter values exhibits a scaling relationship governed by the largest-in-magnitude Floquet multiplier, here required to be positive and real, in complete agreement with the characteristic scaling observed in the numerical study. A similar cascade is predicted and observed in the case of a saddle–node bifurcation of a period-two orbit, away from the discontinuity, provided that the associated center manifold is found to intersect the discontinuity transversally.

1. Introduction

Piecewise-defined maps are a subject of increasing scientific interest, particularly as a description of global dynamics in piecewise-smooth flows. A piecewise-defined map is defined smoothly only over the interior of a partition of its domain, with discontinuities and/or loss of differentiability on the boundaries of this partition. When a map is derived as a stroboscopic snapshot of a flow, discontinuities are often the result of tangential (*grazing*) contact between the flow and a hypersurface at which a discontinuity in the vector field or the instantaneous state is introduced. In the neighborhood of grazing contact, small perturbations cause the forward dynamics to either intersect the hypersurface, or miss it, creating a corresponding discontinuity in the global dynamics. Well-known examples of piecewise-defined maps pertaining to grazing arise in the mechanics of impact and fluid layer contact. Piecewise-defined maps have been studied in their own right, for example in models of heart arrhythmia, neuron firing, and electrical power converters; see di Bernardo et al. [1] for a review.

The application focus of this paper is on hybrid dynamical models of the cell cycle of budding yeast (cf. Li et al. [2], Pfeuty and Kaneko [3], Tyson and Novák [4], and Qu et al. [5], but see also Noel et al. [6] and Alfieri et al. [7] for the construction of switched models of the cell cycle) designed to replicate experimentally observed processes of eukaryotic cell growth. In these models, the growth cycle exhibits exponential increase of cell mass, accompanied by variations in activator and inhibitor protein concentrations, modeled by a set of coupled nonlinear ordinary differential equations. When the concentration of a key protein falls below a critical value, the models considered here assume an essentially instantaneous cell division (mitosis) event, resulting in two progeny cells, each carrying a fraction of the mass of the mother cell. A period-p orbit represents a periodic sequence of p

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* Corresponding author.
E-mail address: danko@illinois.edu (H. Dankowicz).

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cycles of cell growth over which the mass at mitosis assumes p different values. In particular, period-one orbits result in regular cell cycles where the mass at mitosis is the same each time.

A *discontinuity-induced bifurcation* [1] occurs in a piecewise-smooth system, when the presence of a discontinuity results in a bifurcation that is unanticipated by the local description of the flow about some reference trajectory in the case that the discontinuity were to be ignored (without destroying the existence of the reference trajectory). In the cell-cycle models, an obvious example of a discontinuity-induced bifurcation is the disappearance (under further parameter variations) of a period-p orbit when the state during one of the cell cycles grazes the division threshold. A local analysis of return maps near such a grazing orbit yields a piecewise-defined map that is discontinuous across some hypersurface of initial conditions. In the piecewise-affine case, such a "map with a gap" (see Hogan et al. [8]) is known to exhibit complicated bifurcation scenarios, including period-adding cascades, period-incrementing cascades, and robust chaotic attractors (e.g., Dutta et al. [9], Rajpathak et al. [10], but see also Glendinning [11] and Keener [12] for an analysis of routes to chaos in general piecewise-defined maps).

In the present paper, we derive a small set of sufficient conditions for the existence of period-adding bifurcation cascades accumulating on a grazing bifurcation of a period-two orbit in such piecewise-defined maps and verify the theoretical predictions using careful numerical analysis of suitably-constructed boundary-value problems for the cell cycle models. The theoretical analysis is found to accurately describe cascades observed in the numerical analysis of the corresponding hybrid dynamical system models, both qualitatively and quantitatively, including the prediction of a characteristic scaling relationship. Although this relationship results from the essentially one-dimensional nature of the bifurcation cascade sufficiently close to the accumulation point, the analysis is independent of model dimension and does not require the reduction to a piecewise-defined one-dimensional map.

We further derive a similar set of sufficient conditions for the existence of a period-adding bifurcation cascade accumulating on a saddle–node bifurcation of a period-two orbit, with no point of grazing contact with the system discontinuity. Remarkably, although the saddle–node bifurcation is not induced by the discontinuity, the associated bifurcation cascade is very much a result of the presence of the discontinuity. We here find a discontinuity-induced bifurcation scenario that is triggered by a saddle–node bifurcation, specifically, a saddle–node point on an infinite-period orbit that intersects the discontinuity transversally. We are not aware of any existing treatment or observation of such a global bifurcation scenario in a piecewise-smooth dynamical system.

A key ingredient of the conditions that hold at the accumulation points of the period-adding bifurcation cascades is the reinjection of a neighborhood of a grazing point on the discontinuity into the basin of attraction of the period-two orbit by the application of a state reset. This reinjection persists qualitatively even after the period-two orbit is destroyed by the discontinuity, but the asymptotic convergence to the locus of the period-two orbit (had the discontinuity been ignored) is interrupted by a crossing of the discontinuity and another global excursion away from the discontinuity. The scenario is reminiscent of examples of intermittency and bursting in the literature (cf. Dias De Deus et al. [13] and Mosekilde et al. [14]), but the dependence of the frequency of bursting on the parameter deviation from the accumulation point in the cascade may differ. A similar "homoclinic" behavior, with identical implications to the existence of a period-adding cascade may be found in Budd and Piiroinen [15].

In the remainder of this paper, we introduce and explore numerically two models of the yeast cell cycle in Section 2 and develop the corresponding theoretical treatment in Section 3. In Section 4, we present examples of the phenomenology in the case of piecewise-affine, one-dimensional (complete treatment) and two-dimensional (numerical example) maps, piecewise-nonlinear one-dimensional maps (numerical example), and an autonomous linear oscillator with state resets (numerical example). A concluding discussion in Section 5 reflects on the implications of the analysis to general piecewise-smooth dynamical systems and the class of cell cycle models considered herein.

2. Cascades in models of the yeast cell cycle

2.1. Model formulation

We ground the theoretical analysis of this paper in the context of finite-dimensional, deterministic models of the cell cycle of budding yeast, and establish in these models several realizations of the abstract framework considered in the second half of the paper.

To this end, let u_i, for $i = 1, \ldots, 8$, represent nondimensionalized concentrations of eight key proteins that activate or inhibit different processes in the cycle of growth and division of eukaryotic cells, including the production or degradation of other members of this group of proteins. Specifically, following Tyson and Novák [4], let the continuous-time evolution of the cell state be governed by the following system of differential equations

$$\dot{u}_1 = k_1 - (k_2' + k_2''u_2 + k_2'''u_4)u_1, \tag{1}$$

$$\dot{u}_2 = \frac{(k_3' + k_3''u_4)(1-u_2)}{J_3 + 1 - u_2} - \frac{(k_4 m u_b + k_4' u_7)u_2}{J_4 + u_2}, \tag{2}$$

$$\dot{u}_3 = k_5' + k_5''\frac{(mu_b)^n}{J_5^n + (mu_b)^n} - k_6 u_3, \tag{3}$$

$$\dot{u}_4 = \frac{k_7 u_5 (u_3 - u_4)}{J_7 + u_3 - u_4} - \frac{k_8 M u_4}{J_8 + u_4} - k_6 u_4, \tag{4}$$

$$\dot{u}_5 = k_9 m u_b (1 - u_5) - k_{10} u_5, \tag{5}$$

$$\dot{u}_6 = k_{11} - (k_{12}' + k_{12}''u_7 + k_{12}'''mu_b)u_6, \tag{6}$$

$$\dot{u}_7 = k_{13}' + k_{13}''u_8 - k_{14}u_7, \tag{7}$$

$$\dot{u}_8 = \frac{(k_{15}'m + k_{15}''u_7)(1-u_8)}{J_{15} + 1 - u_8} - \frac{(k_{16}' + k_{16}''mu_b)u_8}{J_{16} + u_8}, \tag{8}$$

where

$$u_b = u_1 - \frac{2u_1u_6}{\Sigma + \sqrt{\Sigma^2 - 4u_1u_6}} \tag{9}$$

and

$$\Sigma = u_1 + u_6 + \frac{1}{K_{eq}}, \tag{10}$$

and where the nondimensionalized cell mass is governed by the logistic growth model

$$\dot{m} = rm\left(1 - \frac{m}{\bar{m}}\right) \tag{11}$$

with carrying capacity $\bar{m}$. Moreover, suppose that a transversal intersection of the continuous-time trajectory with the zero-level surface of the scalar-valued function

$$h_{\text{mitosis}}(u) := u_1 - \bar{u}_1, \tag{12}$$

in the direction of decreasing values of h_{mitosis}, results in the instantaneous state reset

$$m \mapsto \rho m, \quad 0 < \rho < 1 \tag{13}$$