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Asymptotic periodicity in networks of degrade-and-fire oscillators

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HIGHLIGHTS

- We give mathematical results on dynamics of networks of degrade-and-fire oscillators.
- The model eludes standard assumptions on evolution equations, such as monotonicity.
- We prove convergence to periodic behavior under mild assumption on firing sequence.

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ABSTRACT

Networks of coupled degrade-and-fire (DF) oscillators are simple dynamical models of assemblies of interacting self-repressing genes. For mean-field interactions, which most mathematical studies have assumed so far, every trajectory must approach a periodic orbit. Moreover, asymptotic cluster distributions can be computed explicitly in terms of coupling intensity, and a massive collection of distributions collapses when this intensity passes a threshold. Here, we show that most of these dynamical features persist for an arbitrary coupling topology. In particular, we prove that, in any system of DF oscillators for which in and out coupling weights balance, trajectories with reasonable firing sequences must be asymptotically periodic, and periodic orbits are uniquely determined by their firing sequence. In addition to these structural results, illustrative examples are presented, for which the dynamics can be entirely described.

1. Introduction

To predict the long-term behavior in networks of interacting units is a predominant challenge in nonlinear science, with applications in many disciplines, from physics to biology and to the social sciences, to cite a few examples [1]. In particular, a recurrent question is to characterize collective properties such as synchronization and predictability in terms of the network topology and interaction strengths [2,3]. While this problem has received considerable attention from theoreticians, mathematically rigorous descriptions of (global) nonlinear behavior are scarce, and only address limited circumstances, *e.g.* weak-coupling regimes [4] and assemblies of pulse coupled oscillators with excitatory coupling [5–7]. Hence, the theory remains largely incomplete and network phenomenology still lacks a comprehensive rigorous footing.

In the last years, a model for the population dynamics of simple gene oscillators was introduced [8], inspired from a series of experiments on colonies of synthetic genetic circuits [9,10], and resulting from the simplification of more standard delay-differential equation models [11]. In a few words (see Section 2 for more details), it consists of a collection of pulse coupled oscillators with inhibitory coupling, and is reminiscent of the well-known integrate-and-fire model in neuroscience; however, the phenomenologies of each are distinct.

In the case of mean field coupling, a mathematically rigorous global description of the dynamics, notably its clustering and asymptotic properties, was achieved for every parameter value and for arbitrary numbers of oscillators (and also for the continuum approximation) [12,8]. Analogous features were also described for trajectories issued from typical random initial conditions [13]. In addition, a recent study expanded the analysis to a more elaborate model that involves a global activator field in the dynamics [14]. Motivated by including more realistic features in the mathematical analysis, the current paper aims to extend previous (deterministic) results to arbitrary coupling topologies on populations of arbitrary size.

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A typical property of degrade-and-fire models is their firing process (accompanied with gene level resetting) that occurs when the repressor field becomes (locally) negligible and can no longer prevent gene expression. (Instantaneous resets are used here as a naive representation of massive gene expression during a tiny interval of time.) In the case of mean field coupling, after cell *i* has fired, every other cell (not simultaneously firing with *i*) must fire once, before *i* fires again. The ordering in which cells fire does not change from cycle to cycle (unless cells synchronize and begin firing together). More importantly, this periodic and exhaustive cycle of firings imposes asymptotic periodicity on the trajectories themselves.

While periodic exhaustive firing may not always hold for an arbitrary coupling topology (examples will be provided below), the main result of this paper (Theorem 5.1) states that, when this is the case, the trajectory must asymptotically approach a periodic configuration, provided that all cells are path-wise connected through coupling and in and out weights balance at every node. Even though this conclusion does not *a priori* cover all trajectories of degrade-and-fire systems, it proves that a sufficiently regular firing behavior implies a regular asymptotic behavior of the trajectories themselves, under a mild restriction on the coupling structure. Together with the analysis of orbits with symmetric components, this result paves the way to a comprehensive understanding of the functioning of arbitrary systems of coupled DF oscillators.

The paper is organized as follows. The DF model of N-oscillators is defined in Section 2 and global well-posedness of the dynamics is proved. In Section 3, we study properties of the firing events, and use these features to introduce non-degenerate trajectories with exhaustive firing sequences; such trajectories are at the center of attention in the rest of the paper. In Section 4, we prove that there can be at most one periodic orbit associated with each such sequence, and provide examples of existence and non-existence, in the case of nearest neighbor coupling. Section 5 contains Theorem 5.1 and its proof, while the paper is completed, in Section 6, with a study of the full dynamics for $N = 2$ and $N = 3$ cells (assuming some coupling symmetry in the latter case).

2. The degrade-and-fire dynamics

We consider the degrade-and-fire (DF) dynamics of single self-repressor genes in a colony of cells, driven by intercellular coupling [8]. In this context, cells are indexed by $\{1, \dots, N\}$ (where $N \in \mathbb{N}$) and gene expression levels at time $t \in \mathbb{R}^+$ are represented by the vector $x(t) = (x_i(t))_{i=1}^N \in [0, 1]^N$. Intercellular coupling of genes in this population is mitigated by a repressor field $Wx = (Wx_i)_{i=1}^N$, defined as the action of the linear operator W on the vector x,

$$Wx_i = \sum_{j=1}^{N} w_{ij}x_j, \quad \forall i \in \{1, \dots, N\},$$

where the symbol $W = (w_{ij})_{i,j=1}^N$ also denotes a stochastic non-negative matrix. The dynamics depends as well on a threshold parameter $\eta \in (0, 1)$, which is assumed to be small. Finally, we impose that the matrix diagonal terms satisfy $w_{ii} > \eta$ for all i. (NB: Ref. [8] assumed **mean field** coupling, *viz.* $Wx_i = (1-\epsilon)x_i + \frac{\epsilon}{N}\sum_{j=1}^N x_j$ for all i.) Here, we consider for now any coupling satisfying the condition $w_{ii} > \eta$ for all $i \in \{1, \dots, N\}$, and later impose additional constraints when asymptotic periodicity is investigated.

With these definitions in place, the DF time evolution of gene expression levels is given by the following differential equation, inspired by the delay-differential equation model in [11]:

$$\begin{aligned} &\dot{x}_i(t) = -\mathrm{Sgn}(x_i(t)) && \text{if } Wx_i(t) > \eta, \\ &\begin{cases} x_i(t) = x_i(t-0) \\ x_i(t+0) = 1 \end{cases} && \text{if } Wx_i(t) \leq \eta. \end{aligned} \qquad (1)$$

In other words, the dynamics in cell i consists of two phases, depending on the repressor field $Wx_i(t)$.

- When $Wx_i(t) > \eta$, the expression level $x_i(t)$ **degrades** at constant speed -1, unless it has reached zero (in which case, it remains at zero). In this phase, if we also have $x_j(t) > 0$ for all cells j such that $w_{ij} > 0$ (called influencing cells), the repressor level $Wx_i(t)$ also decreases with speed 1. We may eventually have $Wx_i(t) \leq \eta$, depending on expression level behaviors in influencing cells.
- When $Wx_i(t) \leq \eta$, a **firing** takes place and resets the expression level to the value 1. The assumption $w_{ii} > \eta$ ensures that $Wx_i(t + 0) > \eta$ for the repressor field in cell i after resetting. Hence, after every firing, the reset genes return to the degrade phase for a positive-length time interval.

Accordingly, the behavior in each cell consists of an eternal succession of degrading phases interrupted by instantaneous firing, unless the repressor level becomes sufficiently high to prevent any further firing and to maintain the gene level in a vanishing stationary state.

Prior to investigating these behaviors in more detail, we first make sure that the dynamics is globally well-posed. As the next statement shows, this is granted by assuming that the evolution begins with a degrading phase in every cell. An element $x \in [0, 1]^N$ is said to be **admissible** if $Wx_i > \eta$ for all $i \in \{1, \dots, N\}$. (NB: any $x \in [\eta, 1]^N$ is admissible.)

Lemma 2.1. *For any admissible* $x \in [0, 1]^N$, *Eq.* (1) *has a unique global solution such that* $x(0) = x$.

Proof. Local existence is a direct consequence of the admissibility condition. Moreover, we have $x_i(t) = (x_i - t)^+$ for all i, provided that $t \geq 0$ is sufficiently small. In fact, this expression holds up until a firing occurs.

In addition, for every solution of (1), the function $t \mapsto Wx_i(t)$ is left continuous in every cell; hence we must have $Wx_i(t) \geq \eta$ for all (i, t) (see Lemma 3.1 in [12]). Accordingly, the first time t_1x when a firing occurs, *viz.* the first **firing time**, is given by

$$t_1x = \inf\{s > 0 : Wx_i(s) = \eta \text{ for some } i \in \{1, \dots, N\}\}.$$

Clearly, we have $t_1x < +\infty$ (and the infimum here is actually a minimum).

Let the **firing map** F be defined on admissible vectors $x \in [0, 1]^N$ by $Fx = x(t_1x + 0)$. The assumption $w_{ii} > \eta$ implies that Fx is also admissible. Hence the second firing time $t_2x = t_1 \circ Fx$ is also well-defined and we have $x_i(t) = (Fx_i - t + t_1x)^+$ for $t \in (t_1x, t_2x]$. By induction, one obtains an infinite sequence $\{t_kx\}_{k\in\mathbb{N}}$ of firing times and a unique well-defined solution on every interval $(t_kx, t_{k+1}x]$.

To conclude, it remains to show that $\lim_{k\to+\infty} t_kx = +\infty$. Assume for the sake of contradiction that $t_\infty = \lim_{k\to+\infty} t_kx < +\infty$. By the Pigeonhole Principle, there exist $i \in \{1, \dots, N\}$ and a subsequence $\{k_n\}_{n\in\mathbb{N}}$ such that $Wx_i(t_{k_n}x) = \eta$ for all n and $\lim_{n\to+\infty} t_{k_n}x = t_\infty$. For this i, the expression $x_i(t_{k_{n+1}}x) = \left(1 - t_{k_{n+1}}x + t_{k_n}x\right)^+$, together with the characterization of the firing time $t_{k_{n+1}}x$, implies the estimate

$$\eta = Wx_i(t_{k_{n+1}}x) \geq \left(1 - t_{k_{n+1}}x + t_{k_n}x\right)^+ w_{ii}.$$

Using that $\lim_{n\to+\infty} t_{k_{n+1}}x - t_{k_n}x = 0$, we conclude that $\eta \geq w_{ii}$, contradicting the original assumption on the self-influencing weights w_{ii}. □