Regulatory Networks and Cellular Rhythms

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Rhythmic phenomena occur at all levels of biological organization, with periods ranging from a fraction of a second to years. Many rhythms originate from the regulatory feedback loops that control the dynamics of cellular processes. Cellular rhythms provide a prototype for the field of Systems Biology as they illustrate how an emergent property, autonomous oscillatory behavior, arises from molecular interactions in regulatory networks [1]. Oscillations can best be addressed by combining an experimental with a modeling approach. After providing an overview of biological rhythms, I will focus on two major examples of rhythmic behavior in cellular regulatory networks: circadian clocks and the cell cycle. First, computational models will be used to address the molecular mechanism of circadian rhythms, as well as the dynamical bases of circadian clock-related physiological disorders [2,3]. Second, using a model for the enzymatic network of cyclin-dependent kinases (Cdks) that drives the mammalian cell cycle I will show that the regulatory structure of the Cdk network results in its temporal self-organization in the form of sustained oscillations, leading to the sequential activation of the Cdks that brings about the orderly progression along cell cycle phases [4-6]. The coupling of the cell cycle to the circadian clock results in the synchronization of these two major cellular rhythms [7].

1. A. Goldbeter, C. Gérard, D. Gonze, J.-C. Leloup and G. Dupont, Systems biology of cellular rhythms. *FEBS Lett*. **586**, 2955-2965 (2012).
2. J.-C. Leloup J-C and A. Goldbeter, Toward a detailed computational model for the mammalian circadian clock. *Proc. Natl. Acad. Sci. USA,* **100**, 7051-7056 (2003).
3. J.-C. Leloup and A. Goldbeter, Modeling the circadian clock: From molecular mechanism to physiological disorders. *BioEssays* **30,** 590-600 (2008).
4. C. Gérard and A. Goldbeter, Temporal self-organization of the cyclin/Cdk network driving the mammalian cell cycle. *Proc. Natl. Acad. Sci. USA* **106**, 21643-21648 (2009).
5. C. Gérard and A. Goldbeter, From quiescence to proliferation : Cdk oscillations drive the mammalian cell cycle. *Front. Physiol*. **3:**413 (2012).
6. C. Gérard and A. Goldbeter, The cell cycle is a limit cycle. *Math. Model. Nat. Phenom*. **7**, 126-166 (2012).
7. C. Gérard and A. Goldbeter, Entrainment of the mammalian cell cycle by the circadian clock : Modeling two coupled cellular rhythms. *PLoS Comput. Biol*. **8 (5)**: e1002516 (2012).