MAR08-2007-005624
Abstract for an Invited Paper
for the MAR08 Meeting of
the American Physical Society

Stability and Noise in the Cyanobacterial Circadian Clock

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Accuracy in cellular function has to be achieved despite random fluctuations (noise) in the concentrations of different molecular constituents inside and outside the cell. Single cell in vivo monitoring reveals that individual cells generate autonomous circadian rhythms in protein abundance. In multi-cellular organisms, the individual cell rhythms appear to be noisy with drifting phases and frequencies. However, the whole organism is significantly more accurate, the temporal precision being achieved most probably via intercellular coupling of the individual noisy oscillators. In cyanobacteria, we have shown that single cell oscillators are impressively stable and a first estimation rules out strong intercellular coupling. Interestingly, these prokaryotes also have the simplest molecular mechanism at the heart of their circadian clock. In the absence of transcriptional activity in vivo, as well alone in vitro, the three clock proteins KaiA, KaiB and KaiC generate a self-sustained circadian oscillation of autophosphorylation and dephosphorylation. Recent chemical kinetics models provide a possible understanding of the three-protein oscillator, but the measured in vivo stability remains yet unexplained. Is the clock stability a built-in property for each bacterium or does a weak intercellular coupling, make them appear like that? To address this question we first theoretically designed our experiment to be able to distinguish coupling, even weak, from phase diffusion. As the precision of our evaluation increases with the length of the experiments, we continuously monitor, for a couple of weeks, mixtures of cell populations with different initial phases. The inherent experimental noise contribution, initially dominant, is reduced by enhanced statistics. In addition, in situ entrainment experiments confirm our ability to detect a coupling of the circadian oscillator to an external force and to describe explicitly the dynamic change of the mean phase. We report a value of the coupling constant that is small compared to the diffusion constant. These results therefore confirm that the cyanobacterial clock stability is a built-in property: the cyanobacterian clock mechanism is not only the simplest but also the most robust.