signalling is important for timely SIN resetting (Figure 2). Globally, their model proposes that etd1p is required for SIN activation, but that the active SIN in its turn inactivates etd1p, perhaps by promoting its degradation. During anaphase, the balance initially favours etd1p, and it promotes an increase in SIN activity. At the time of septum formation when etd1 expression declines [6], the active SIN gains the upper hand, and etd1p activity declines. As etd1p is required for SIN activity, SIN signalling from the nSPB after cleavage, consistent with a delay in resetting the SIN. Filming of dikaryons suggests that SIN asymmetry is required for the differential changes in etd1p level that are observed in the daughter cells. The mechanism whereby closure of the contractile ring is coupled to SIN inactivation remains to be elucidated. This study does not address what establishes the initial SIN asymmetry in anaphase B, though cdc inactivation is clearly important [13,14].

In SIN mutants, the GAP remains asymmetric [15,16], suggesting that the establishment of SIN protein asymmetry is mediated via the GAP, though this remains conjectural.

In summary, this paper [3] sheds new light on SIN regulation and builds upon the earlier proposition [6] that etd1p degradation could be coupled to SIN inactivation, incorporating a role for the mitotic asymmetry of the SIN proteins. Understanding how the mutual regulation of etd1p and the SIN works will be of great interest. We speculate that if etd1p activates the SIN, then perhaps the contractile ring-dependent medial pool of GFP–etd1p observed in early mitosis [6] contributes to the SIN’s early mitotic activity in contractile ring formation. Finally, we note that the observation that the progeny of a single division differ with regard to their treatment of GFP–etd1p provides another instance of an asymmetric event in the ‘symmetric’ fission yeast cell, which include the regulation of mating-type switching [17], maturation of spindle pole bodies over two cell cycles [4], and the growth pattern and segregation of cell polarity factors [18]. It will be of interest to determine whether the SPB inherited by a cell affects any other aspects of its biology.

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Circadian Clocks: Evolution in the Shadows

As scientists, we strive for highly controlled conditions. The real world, however, is noisy. Complex networks are a coping mechanism for an erratic environment.

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The field of genetics has elaborated a multitude of partially defined complex networks. An excellent example is the molecular mechanism driving the circadian biological clock (Figure 1). The clock is a fundamental process that permeates biology at all levels, creating a temporal structure that serves to anticipate what is needed by the cell and the organism, and when. Originally characterized as a simple, single feedback loop, the molecular circadian network is presently described as a collection of transcription factors that form interlocked loops [1]. In an attempt to understand the inherent complexity of the circadian clock, a group of systems biologists, as reported in this issue of Current Biology, has applied (relatively) unbiased iterative modeling to the
problem of network evolution [2]. For their simulations, Troein et al. [2] fed the model alternatively with either smooth, square-wave or noisy (i.e., realistic) information to evoke daily light cycles. They asked what kinds of networks would arise and they discovered that features of the light environment that derive from real weather as well as day length promote complexity.

The molecular clock has been largely defined using free-running, self-sustained oscillation as an assay despite the fact that the clock is always entrained or synchronized in nature to cycling conditions. Throughout evolution, the clock has been shaped by zeitgeber (from the German for ‘time-giver’) cycles that are repetitive with respect to day and season. Light is generally considered the most important zeitgeber [3], and it is certainly the best characterized for its effects on circadian clocks, albeit most often in the form of a discrete light pulse.

An important aspect of the light environment, however, is day length, which regulates, for example, reproduction via the circadian clock [4]. Photoperiod can be predicted to the minute for centuries past and to come; however, over the day, the light environment can change from one minute to the next (for example, via cloud cover; Figure 2). At least for plants and animals, an indication of the mechanism of biological photoperiodism is the expression of key clock genes around dawn and dusk, irrespective of the day length [5,6]. The induction of an RNA species at dawn could be caused by a simple light induction, but for gene expression to anticipate dusk in different photoperiods demands a sophisticated timing mechanism. The function of the circadian system is to provide a reliable temporal structure (hence the word ‘clock’) according to photoperiod and despite a light environment that can change from day to day or even within a day. Indeed, earlier modeling experiments have demonstrated that noise can serve a stabilizing function in a network of feedback loops [7].

The experiment that Troein et al. [2] performed began with an unspecified network of four genes. Interaction between any two components or even feedback on self was allowed; delays were included as parameters that could be modified, a feature that would allow some in silico post-transcriptional regulation, thought to be necessary to achieve a 24 hour oscillation. Any of the genes could be regulated by a light signal, although one component was specified as the dawn component and the other as the dusk one; they had to be expressed in specified time windows relative to the photoperiod. Simulations were run ‘under entrainment’ in conjunction with various selection procedures (fitness testing and pruning to keep the number of feedbacks somewhat constrained). The resulting networks increased in interconnectedness as the entrainment moved from single photoperiod to multiple photoperiods, but only the combination of various photoperiods together with a realistic, noisy light environment — actually derived from a year of recordings in the Harvard Forest — yielded a highly interconnected network, showing that complexity is an outcome of real weather.

Many interesting implications flow from this work. One of these concerns how light is taken up by the circadian clock. Both the timing and amount of light administered can change the phasing of clock-regulated processes [8]. Hence, understanding how light acts on the clock is as important as understanding the clock mechanism itself. The input pathway is the first step in the process and, although a number of photoreceptor molecules are known for plants, animals and fungi [9–13], signal transduction leading from outer to inner worlds is poorly filled in. For instance, while it was once thought that light acted by acutely inducing clock gene RNAs [14], it was later demonstrated that the RNAs and translation of their proteins are differentially regulated by light in entrainment [15]. Recent work using mice suggests that it is primarily the chronic rather than acute effects of light that are determining entrained phase (when in the day an individual is active) [16]. This observation should change our concepts of entrainment, which have previously been built on the assumption of rapid, discrete phase shifts. Modeling (perhaps even the models derived here) could be used to predict key features of light signaling to the clock network that meet both the demands and constraints of the biological system and the reality of the physical environment.

Second, the modeling suggests that a non-noisy light environment fails to stimulate development of a network that shows a self-sustained, oscillating rhythm in constant conditions. This feature is often considered to be a hallmark of a circadian clock. One problem with equating free running rhythms with a clock is that a failure to find rhythmicity could represent an experimental failure rather than a bona fide absence of a biological clock. In support of this line of reasoning is the systematic circadian entrainment that can be demonstrated in some mutants that do not show a robust free running rhythm [17]. The model that Troein et al. [2] generated with simple, square wave photoperiods as light cycles manages to show circadian entrainment, as

![Figure 1. Eukaryotic circadian clock networks.](image-url)
different sorts of climates. For instance, the period of the free running rhythm at different incubation temperatures or qualities of the entrained phase might be more or less stable, reflecting compensation mechanisms of the metabolic networks to noise. The model also predicts that self-sustained rhythms would be less common in organisms from less noisy environments.

Finally, in the era of systems biology and genetics, the phenomenon of complex regulatory networks, similar to what has been discussed here, is not unusual. The principles that apply to an evolving circadian network might also apply to other networks, such as the cell cycle or developmental pathways. The prediction is that complexity contributes to compensation mechanisms: namely, it contributes robustness against noise from the inner and outer worlds. This generalization might be applied towards understanding functional attributes of (non-clock) networks.

“If you don’t like the weather, just wait a few minutes” is a well-known adage to New Englanders. We (the authors) live in the Netherlands, where they say “Kermis in de hel” (it’s a carnival in hell), referring to occasionally unpredictable and simultaneously conflicting weather conditions. In much of the world — at least in the temperate zones — the natural zeitgeber cycle is rife with interference due to weather. Complexity in genetic networks will serve to preserve biological function in the face of reality, which is erratic.

References


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