Patterning in Bacteria

Spatial Regulators for Bacterial Cell Division Self-Organize into Surface Waves in Vitro
Science 320 *789-792 (2008)*
Martin Loose, Elisabeth Fischer-Friedrich, Jonas Ries, Karsten Kruse and Petra Schwille

Recommended with a commentary by Martin Howard, The John Innes Centre, UK

How can highly intricate spatiotemporal order be achieved within a biological cell? This question is central to cell biology, and is clearly an issue where biological physicists can make a telling contribution. Understanding of far from equilibrium patterns in physical systems is now relatively advanced after decades of study. The same cannot be said for pattern formation in the biological arena. Although some key theoretical ideas are well established (Turing patterns, morphogen gradients), the tremendous diversity of shape and form in biology ensures that much remains to be discovered. Moreover, rigorous quantitative experimental tests even of our existing theories for biological pattern formation are few and far between.

One tempting target for the study of patterns in biology is in bacteria. Although such organisms are small (and hence internal patterning is hard to see), the (relative) simplicity of their organisation compared to more sophisticated cells makes them attractive objects of study. Up until a decade or so ago, however, the prevailing view of bacteria was one of featureless bags of enzymes with little internal spatiotemporal order. This view has now been comprehensively debunked by the revolution in fluorescent imaging technology. Instead, we now know that bacteria are exquisitely ordered on sub-micron length scales, with many specific structures being precisely placed in space and time within a single cell.

A paradigmatic example of this order is provided by the Min system of proteins that regulate cell division positioning in the rod-shaped bacterium *E. coli* [1]. Getting the site of cell division right is obviously an important goal for all cells: mistakes mean that the chromosomes may not be properly segregated into both daughter cells, with disastrous consequences. Bacteria have therefore evolved mechanisms to place their site of division with great precision. In *E. coli* the Min proteins perform this role. Surprisingly it was found about a decade ago that the Min system actually constitutes a spatiotemporal oscillator, with the proteins coherently oscillating from end to end of the cell with a period of about a minute [2]. As a result of the oscillations the Min proteins have (on time-averaging) high concentrations at the cell ends with low concentrations at mid-cell. Since the downstream proteins of the division apparatus are sensitive to the Min concentrations, the division apparatus will tend to accumulate where the Min concentration is lowest, namely at mid-cell. However, this reasoning does not help to uncover the fundamental mechanism behind the oscillations.

To understand the mechanism, a theoretical analysis is called for. At about the same time, several groups independently proposed that the Min oscillations were the result of a dynamic instability [3-5]. The net effect of the interactions between the Min proteins, both in the cytoplasm and on the cell membrane, together with their diffusion and hydrolysis of Adenosine triphosphate (ATP), renders a homogeneous concentration profile unstable to perturbations. Although the exact details of the instability differ (Turing-type [3], a number-conserving reaction-diffusion instability [4], and an instability induced by attractive Min interactions on the membrane [5]), the fundamental concept of self-organised non-equilibrium pattern formation was in all cases similar. Subsequent elaborations of these models now produce predictions in good agreement with experiments. However, why a spatiotemporal oscillator has been selected to determine the site of division (rather than, say, a static concentration gradient) is still mysterious.

Can we now subject these models to a more controlled and rigorous testing? One unambiguous prediction of the models was that to generate dynamics one requires only a very small number of ingredients. In particular, two of the Min proteins (MinD and MinE) would be needed, together with lipid to which the proteins can bind, and a supply of ATP to drive the non-equilibrium dynamics. It is this prediction that has now been tested in a beautiful series of experiments by Loose *et al*. Using an *in vitro* set-up with only the above 4 purified components, they observed travelling waves (see Fig. 1), and in some instances rotating spirals, of the Min proteins. Observing waves rather than oscillations is to be expected due to the open nature of the experimental system, and overall provides strong support for previous modelling. However, the quantitative agreement between existing theories and the *in vitro* experiments was not good and this points the way towards further improving our theoretical understanding of the system. In particular, Loose et al suggest that cooperative binding of MinE to the membrane is an important component of the Min dynamics.

In vitro reconstitution is clearly a powerful tool to probe the dynamics of simple biological systems, as exemplified by its application to the Min system. These experiments also demonstrate one route to making biology more quantitative, thereby subjecting our theoretical ideas to sterner tests than standard, somewhat qualitative, biological experimentation. Often our theories will come up short in this exacting contest, but that will just show how much we still have to learn about patterning in biology.

1. Lutkenhaus J, Annu Rev Biochem 76 539 (2007)
2. Raskin DM and de Boer PAJ, Proc Natl Acad Sci USA 96 4971 (1999)
3. Meinhardt H and de Boer PAJ, Proc Natl Acad Sci USA 98 14202 (2001)
4. Howard M, Rutenberg AD and de Vet S, Phys Rev Lett 87 278102 (2001)
5. Kruse K, Biophys J 82 618 (2002)

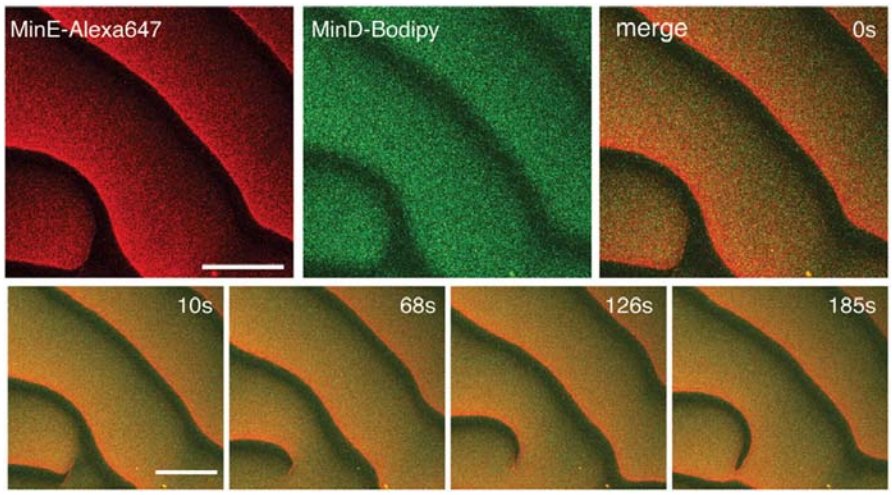

Fig. 1. Min-protein waves *in vitro*. Figure taken from Loose *et al*. Images of protein waves on a lipid membrane, MinD (green), MinE (red). Scale bar, 50 µm.