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that individual costs and risks associated with nonreciprocated empathy and altruism are reduced. By this view, enhanced empathic neural response for same but not other races is a consequence of group selection in prosociality and altruistic behavior. Nevertheless, growing evidence indicates that racial bias in empathic neural responses is not inevitable, but instead results from culturally acquired prejudice. This in turn demonstrates flexibility in empathic neural circuitry and highlights a pivotal role for culture in changing how and when humans share and respond to the suffering of same and other races.

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# Epigenetic Switching: Bacteria Hedge Bets about Staying or Moving

**Growing populations of *Bacillus subtilis* exhibit bistability: motile cells co-exist with long chains of sessile cells. An epigenetic switch has been characterized that controls the transition between the two cell types.**

**Patrick Piggot**

Motility gives bacteria the distinct advantage of being able to move towards good things, and away from bad things. However, considerable resources need to be devoted to building flagella, becoming motile and displaying chemotaxis. Consequently, if local conditions are good, there is an advantage to staying put, and not wasting resources on these processes. Indeed, motility is typically regulated so that bacteria are sometimes sessile and sometimes motile. In *Bacillus subtilis*, these two types of bacterial cell can occur successively or can co-exist as distinct cell lineages within a genetically homogeneous population. A recent paper by Chai *et al.* [1] elucidates the nature of the epigenetic switch between the two lineages. The switch has a double-negative feedback loop involving protein–protein and protein–DNA interactions.

In species such as *Escherichia coli*, motility may be associated with a particular growth phase: the bacteria are not motile during exponential growth in batch cultures, when the times are good, and food is plentiful. They become motile during the transition to stationary phase, bad times with starvation approaching [2]. Similar behavior is exhibited by *B. subtilis* when it is grown in a rich medium [3]. With *B. subtilis*, the non-motile cells are not simply sessile, and devoid of flagella: they are present in long chains because separation of the sessile cells lags far behind their formation by cell division. This behavior means that any switch between non-motile and motile is also a switch between low and high activity of the autolysins responsible for cell separation. In appropriate circumstances, motile *B. subtilis* can go on to initiate formation of biofilms, in which the bacteria have again become sessile, and are in long chains that are held together by an extracellular matrix [4,5].

In the contrasting case of *Caulobacter crescentus*, both motile and sessile bacteria are present throughout exponential growth. Sessile, stalked bacteria grow and divide by binary fission to give one daughter that is motile, with the other being sessile [6]. Thus, after every division half the population stays and half is able to move to better conditions. The sessile daughter is primed to undergo another division; the motile daughter must first differentiate into a sessile cell before it is able to divide. Both sessile and motile bacteria are also observed throughout growth for *B. subtilis* when it is grown in a minimal medium [3,7] (Figure 1). However, the mechanism controlling this bifurcation is very different. Within the same growing population the two

cell types co-exist as distinct lineages: that is to say, the population exhibits bistability [1,7,8]. It is as if *B. subtilis* is hedging its bet about how to respond to future conditions: if conditions turn bad, part of the population can react immediately by swimming away; in contrast, a totally sessile population would take some time before it could assemble flagella and respond [1,8,9].

The autolysins that separate divided cells are 'smart' enzymes: they hydrolyse bonds in peptidoglycan located between the cells, yet ensure that the thick polar peptidoglycan caps of recently separated cells are retained. Autolysin may seem a misnomer — only when regulation has gone awry is there cell lysis (autolysis). However, autolysins must be tightly controlled, or disaster can occur. Transcription of the genes for the main autolysins responsible for cell separation in *B. subtilis* is directed by an alternative σ factor $\sigma^D$, as is transcription of genes for motility and chemotaxis [8]. Transcription of these genes is also controlled by three regulatory proteins, SinI, SinR and SlrR. The interplay of the three regulators is the focus of the paper by Chai *et al.* [1]. In it they elucidate how an epigenetic switch is formed by SinR, SlrR and *slrR*, the gene encoding SlrR: in one state (the ON state) there are isolated cells and cell pairs that are motile; in the other state (the OFF state) there are long chains of cells that lack flagella (Figure 1).

Let us now consider the various parts of this regulatory system. SinI is an anti-repressor that binds to and inhibits the repressor protein SinR. SinR directly represses transcription of *slrR* (and also of genes for biofilm matrix formation). The exciting findings reported by Chai *et al.* [1] start with their observation that SlrR also can bind to SinR. They demonstrate two important consequences of the SlrR–SinR interaction. First, the SlrR–SinR complex, but neither SlrR nor SirR alone, is a potent repressor of transcription of the autolysin genes and of the gene for flagellin, the structural protein of the flagellar filament. Thus, SlrR–SinR triggers the change from motile cells (ON) to sessile chains of cells (OFF). Second, the repressor function of SinR is inhibited by SlrR. As a consequence, transcription of *slrR* is derepressed, thus forming a self-reinforcing loop for SlrR synthesis. The regulatory loop exhibits hysteresis, a characteristic of a bistable switch [1,9]. With low SlrA the switch is ON, with high SlrA it is OFF. This epigenetic ON–OFF switch controls the bistablity of cell separation and motility in growing populations of *B. subtilis*. It joins the select number of examples of bistability that have been characterized in bacteria [5,9].

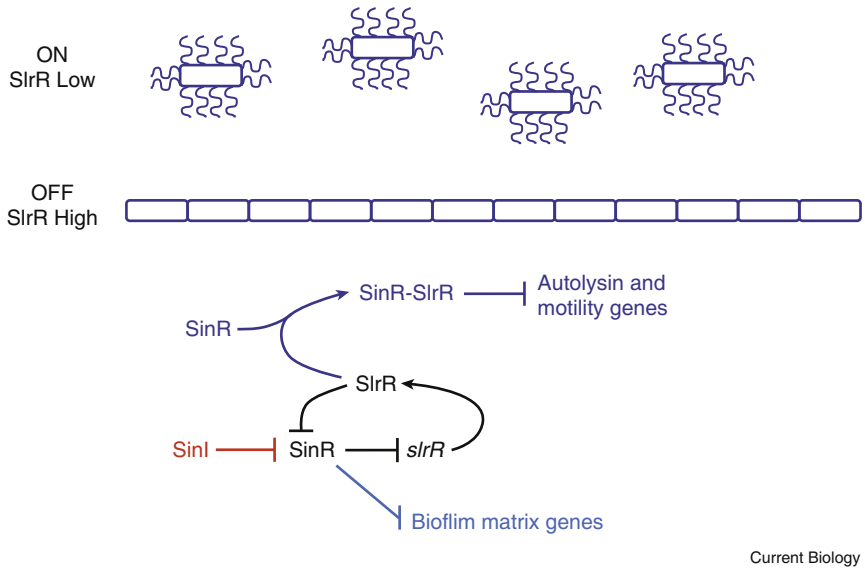


Figure 1. Epigenetic switch controlling cell separation and motility in *Bacillus subtilis*.
The top of the figure illustrates the two epigenetic states: ON, motile cells with peritrichous flagella: OFF, long chains of sessile, aflagellate cells. The epigenetic switch, consisting of the proteins SinR and SlrR and the gene *slrR*, is shown in black. The protein thought to throw the switch, SinI, is shown in red. The switch is ON when the concentration of SlrR is low, and genes for motility and cell separation (autolysins) are expressed. The switch is OFF when the concentration of SlrR is high, sequestering SinR, thus relieving repression of *slrR* and causing repression of the genes for motility and cell separation by the SlrR–SirR complex. (Adapted with permission from [1].)

SinI appears to be the protein that throws the switch. It can do so in two different ways, stochastically and deterministically. During exponential growth, it does so stochastically. It is expressed at low levels, whereas SinR is produced constitutively. This imbalance favors SinR so that the switch is ON (motile cells). However, noise (variability) in SinI expression is thought to be such that the level of SinI is occasionally sufficient to throw the switch to OFF so that bistability ensues. This suggestion is favored by the observation that *sinI* mutants are locked in the ON state, with no bistability; it may be that noise in other components also affects the switch [1]. During the transition to stationary phase, in contrast, the switch is deterministic. The master regulator of the transition state, Spo0A, becomes active, and greatly increases SinI production so that SinR is inhibited (in itself, a complex story [3]). As a consequence SlrR gains the upper hand, and the population is switched to sessile chains. In these circumstances matrix production and biofilm formation result (Figure 1).

Other factors also play a part in this epigenetic switch, but their roles are incompletely understood. ON cells have active $\sigma^D$, and need it to express autolysin and motility genes. OFF cells do not need $\sigma^D$ and contain little of it [4]. The structural gene for $\sigma^D$, *sigD* is the 30$^{th}$ gene in the monstrous 31-gene *fla/che* operon. One of the promoters of the complete operon, and a second internal promoter depend on $\sigma^D$, providing a positive feedback loop that may help stabilize the ON state [8]. More mysterious is the SwrA protein. It is an activator of *fla/che* operon transcription, and there are more OFF cells when *swrA* is inactivated [7,10]. The mystery is that *swrA* inactivation greatly slows the speed of OFF–ON switching. Intriguingly, many laboratory strains of *B. subtilis* have a frame-shift mutation in *swrA*, slowing their switching, and leading to speculation about phase variation [7]. There is more to learn about this ON–OFF switch!

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# Mating-System Evolution: Rise of the Irresistible Males

**Mating-system models have struggled to account for the high frequency of males found with hermaphrodites in a common Mediterranean shrub. The discovery of its unusual self-incompatibility system now provides an elegant and unexpected solution to the puzzle.**

**John R. Pannell and Grazyna Korbecka**

Here's a story that nicely exemplifies the ambivalent role played by theory and 'paradigm' in both resisting and facilitating scientific discovery [1]. The protagonist is *Phillyrea angustifolia*, a self-incompatible, wind-pollinated shrub that is widespread in fire-prone vegetation of the western Mediterranean (Figure 1). *P. angustifolia* has attracted the attention of plant reproductive ecologists for several decades [2–5], because it displays an apparent example of one of the rarest sexual systems known to biology — androdioecy, where males co-occur with hermaphrodites. The interest in *P. angustifolia*, however, lay not so much in the possibility that it might be androdioecious, as in the suspicion that it might not. And if not androdioecy, what else might be going on?

The problem with androdioecy in *P. angustifolia* was that its populations consistently contain too many males. Straightforward models show clearly that males must be less frequent than hermaphrodites in any androdioecious population; indeed, to be maintained at all, males must enjoy more than twice the siring success of hermaphrodites [6,7] (Figure 2). This simple prediction should be intuitive: given that males transmit genes to the next generation only through pollen, whereas hermaphrodites gain reproductive success through the production of seeds as well as pollen, the absence of a female function in males must be compensated for by doubling their male function. The males of *P. angustifolia*, however, do not appear to produce much more pollen than hermaphrodites, and paternity analysis indicates that hermaphrodites sire almost as many progeny as do males [5]. According to theory, therefore, males should be absent in *P. angustifolia*, yet they are often as frequent as hermaphrodites [2,3]. This disagreement between theory and observation cast doubt on whether the species was really androdioecious, and suggested that, instead, it might be cryptic dioecious, with hermaphrodites


Figure 1. *Phillyrea angustifolia* growing in fire-prone vegetation in south-western Portugal. (A) Shrub habit of *P. angustifolia.* (B) Both males and hermaphrodites have axillary inflorescences. (C) Details of its male and hermaphrodite flowers; note the absence of a pistil between the anthers of the male flower (left) and its presence in the hermaphrodite flower (right). Photographs courtesy of Colin Hughes and John Baker.