An externally modulated, noise-driven switch for the regulation of SPI1 in *Salmonella enterica* serovar Typhimurium

Marc Bailly-Bechet · Arndt Benecke · Wolf Dietrich Hardt · Valentina Lanza · Alexander Sturm · Riccardo Zecchina

Received: 3 February 2010 / Revised: 3 November 2010 / Published online: 24 November 2010
© Springer-Verlag 2010

Abstract In this work we consider the regulation system present on the SPI1 pathogenicity island of *Salmonella enterica* serovar Typhimurium. It is well-known that HilA is the central regulator in the overall scheme of SPI1 regulation and directly binds to virulence operons and activates their expression. The regulation of the expression of HilA is via a complex feed-forward loop involving three transcriptional activators: HilC, HilD and RtsA, and the negative regulator HilE. Our aim is to model...
this regulation network and study its dynamical behavior. We show that this regulatory system can display a bistable behavior relevant to the biology of *Salmonella*, and that noise can be a driving force in this system.

**Keywords**  *Salmonella* · Pathogenicity · Regulatory network · Bistability · Noise

**Mathematics Subject Classification (2000)**  92B05 · 37G10 · 34D20 · 34F05

### 1 Introduction

Among bacteria, *Salmonella* serovars are responsible for numerous infections and diseases, ranging from mild gastroenteritis to life-threatening typhoid fever. Infections propagate through contaminated water and food, and the typhoid fever kills more than 600,000 people each year (WHO, 1997). After ingestion, *Salmonella* colonizes the small intestine and is able to internalize into epithelial cells, its first target in the mammalian body. This internalization phase requires the injection of effector proteins into the host cell cytoplasm, which is mediated by a type III secretion system genetically encoded on the so-called *Salmonella* pathogenicity island 1 (SPI1) (Ellermeier and Slauch 2007). Type III secretion systems are needle-like structures which are widespread among bacteria; *Salmonella* contains two of them—encoded within SPI1 and SPI2—which are sequentially activated during infection, one for internalization in epithelial cells and the second for survival and growth within macrophages (Bustamante et al. 2008).

Control of the expression of the SPI1 genetic island is a crucial process during the progress of the infection. The main transcriptional regulator, HilA, encoded itself on SPI1, has been shown to be able to induce the invasion by inducing expression of the *inv/spa* operon (Bajaj et al. 1995). HilA expression itself is regulated by a complex network of activation and repressions, which is able to integrate and filter signals from the environment to activate the internalization process in the correct niche, i.e. the host’s intestine (Altier 2005; Jones 2005). Interestingly, SPI1 expression was found to be bi-stable, yielding “on” and “off” subpopulations under inducing environmental conditions (Ackermann et al. 2008; Hautefort et al. 2003; Temme et al. 2008; Schlumberger et al. 2005) and cooperation between both sub-populations has been proposed to enhance the pathogen’s survival in the infected host (Ackermann et al. 2008). The “on” subpopulation is thought to trigger diarrheal disease, while the “off” subpopulation benefits from the altered environment of the inflamed gut and propagates the genotype. Thus, it was of interest to gain a deeper understanding of the mechanisms regulating SPI1 expression. The central core in this regulatory network is a triangular structure formed by RtsA, HilD and HilC (Ellermeier et al. 2005) (Fig. 1, bold, black arrows). The regulations among these genes and their role in pathogenesis are under intense experimental scrutiny (see e.g. Temme et al. 2008). HilD, HilC and RtsA are thought to form a triangular network system of regulators positively regulating each other, while HilE can regulate this system by acting as a negative regulator of HilD (Fig. 1, ⊥ arrow). In turn, HilD, HilC and RtsA are positive regulators of HilA, the master regulator of SPI1 expression (Fig. 1, grey). Two recent reports