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► **To cite this version:**

Julien Herrou, Tam Mignot. Dynamic polarity control by a tunable protein oscillator in bacteria. Current Opinion in Cell Biology, In press, 62 (1), pp.54-60. 10.1016/j.ceb.2019.09.001 . hal-02459706

**HAL Id: hal-02459706**

**<https://amu.hal.science/hal-02459706>**

Submitted on 10 Feb 2020

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1 **Dynamic polarity control by a tunable protein oscillator in bacteria**

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11  
12 **Keywords:** *Myxococcus xanthus*, MglA, MglB, RomRX, FrzX, FrzZ, oscillator,  
13 polarity, motility

14

15 **Abstract**

16 In bacteria, cell polarization involves the controlled targeting of specific proteins  
17 to the poles, defining polar identity and function. How a specific protein is  
18 targeted to one pole and what are the processes that facilitate its dynamic  
19 relocalization to the opposite pole is still unclear. The *Myxococcus xanthus*  
20 polarization example illustrates how the dynamic and asymmetric localization of  
21 polar proteins enable a controlled and fast switch of polarity. In *M. xanthus*, the  
22 opposing polar distribution of the small GTPase MglA and its cognate activating  
23 protein MglB defines the direction of movement of the cell. During a reversal  
24 event, the switch of direction is triggered by the Frz chemosensory system, which  
25 controls polarity reversals through a so-called gated relaxation oscillator. In this  
26 review, we discuss how this genetic architecture can provoke sharp behavioral  
27 transitions depending on Frz activation levels, which is central to multicellular  
28 behaviors in this bacterium.  
29

## 30 Introduction

31

32 In all three kingdoms of life, cell polarization plays an essential role in many  
33 developmental and cellular processes including molecule transport, cell shape  
34 and differentiation, cell growth and division, motility, and organelle development  
35 and localization. Cell polarity is driven by the asymmetrical distribution of proteins  
36 within a cellular compartment; this asymmetric distribution of proteins enables  
37 polarized functions by establishing a gradient of activity across a cell or the  
38 spatial confinement of an activity to a specific location. Thus, the polarization of a  
39 cell is a dynamic phenomenon, involving the active diffusion and accumulation of  
40 polarized proteins to a precise location [1-6].

41

42 Like many spatially organized organisms, bacterial cells present asymmetrically  
43 distributed polar proteins that vary widely in function. This asymmetric distribution  
44 can be dynamic over time and regulate a number of important cellular processes  
45 including cell division, DNA segregation, cell differentiation and motility etc.  
46 Specific features of the cell poles and the cell envelope facilitate protein  
47 relocalization and accumulation to these regions. Indeed, at the cell extremities,  
48 proteins can be recruited through specific interactions with polar proteins already  
49 present at the cell poles. Protein polarization can also be favored by the low  
50 chromosomal DNA density present in these regions and the curved geometry  
51 and lipid composition of the cell membrane at the poles [2,3,6].

52

53 Cell polarity can be fixed and, for example, dictate the assembly and activity of  
54 specific cellular organelles, such as flagella, pili, stalks etc. [7]. In other  
55 instances, cell polarity is a dynamic process and is intimately associated with  
56 protein movement between poles. These movements can originate from the  
57 activity of biochemical oscillators. The MinCDE system, used by *Escherichia coli*  
58 to define the position of the division septum at mid-cell, is a good example of an  
59 oscillating protein system (Figure 1A). At one pole, MinC forms a complex with  
60 MinD, an ATPase, which associates with the membrane when bound to ATP.  
61 MinC is only active when bound to MinD; its function is to prevent FtsZ ring  
62 polymerization everywhere but the mid-cell and, thus, its polar localization  
63 prevents the formation of aberrant mini-cells. When MinE ring is recruited to the  
64 membrane by MinD, this interaction activates hydrolysis of ATP, resulting in the  
65 dissociation of the MinD cluster from the pole and the release of MinC. After  
66 binding ATP, free MinD rapidly relocates at the opposite pole, and reassociates  
67 with the MinC division inhibitor. Because of the continuous pole-to-pole  
68 oscillation of MinC and MinD, over time, the lowest concentration of MinC is at  
69 mid-cell, allowing division at the cell midpoint only, so that daughter cells are  
70 equivalent in size and shape [3,8,9]. In this system the oscillatory period is  
71 dictated by the slow recruitment of MinE which defines a limiting relaxation step.

72

73 The Cyanobacterial McdAB protein system is another example in which protein  
74 oscillations dictate the localization of protein complexes (Figure 1B). In  
75 Cyanobacteria, specialized compartments called carboxysomes contain essential

76 enzymes for photosynthesis. In *Synechococcus elongatus*, McdA is an ATPase  
77 that interacts with the nucleoid in its ATP-bound form. McdB is a protein that  
78 localizes to carboxysomes and has the ability to directly stimulate McdA ATPase  
79 activity. In its ADP-bound form, McdA is released from the DNA, leading to the  
80 formation of McdA-free regions on the nucleoid. Because McdB is on the  
81 carboxysome and has the propensity to localize at regions rich in McdA, it  
82 promotes the carboxysome relocalization to those regions on the nucleoid. Thus,  
83 the carboxysomes become evenly distributed along the length of a cell. The  
84 McdA oscillations thus arise from the presence of multiple McdB-containing  
85 carboxysomes, causing McdA to repetitively dissociate from and then  
86 reassociate with the nucleoid. Hence, McdB drives emergent pole-to pole  
87 oscillatory patterning of McdA [10,11].

88  
89 A common feature shared by the Min and the Mcd systems is the presence of a  
90 hydrolyzable nucleotide that regulates the interaction and localization of the  
91 oscillating proteins. Thus, MinD and McdA can be considered as molecular  
92 switches that exist in an ATP-bound “ON” state and an ADP-bound “OFF” state.  
93 When bound to ATP, these proteins can form heteromers that are biologically  
94 active [8,10,12,13]. In both examples, gradual activation of ATPase activity  
95 controls the oscillatory period and provokes abrupt transitions in the oscillation  
96 regime.

97 In this review, we describe a novel type of oscillator that, similar to the two  
98 examples above, uses a nucleotide switch to regulate the oscillatory regime, but  
99 that also contains a “gate” modulating the oscillatory regime. In *Myxococcus*  
100 *xanthus*, this system controls the direction of motile cells in response to  
101 environmental cues and allows the formation of complex multicellular patterns.

### 102 103 ***M. xanthus* polarity switch during reversals**

104  
105 *M. xanthus* is a Gram negative rod-shaped Deltaproteobacteria commonly found  
106 in soil and in marine sediments [14,15]. This organism has the ability to prey on  
107 other microorganisms and to form spores embedded in fruiting bodies when  
108 nutrients are scarce in its environment [16,17]. *M. xanthus* has been extensively  
109 studied for its social behavior, its complex life cycle and its motility strategies  
110 [18]. *M. xanthus* cells can indeed adopt a “social” motility (S-motility) or an  
111 “adventurous” motility (A-motility). During S-motility, large groups of cells move in  
112 a coordinated manner, using a form of bacterial “twitching” motility involving the  
113 so-called Type-IVa pili (T4aP) that assembles at the bacterial leading pole  
114 (Figure 2). In this process, the pili are polymerized by a multiprotein apparatus  
115 and bind like “grappling hooks” to a self-secreted exopolysaccharide. After  
116 adhesion, the pili retract by depolymerization, pulling the cell forward [19,20].

117 During A-motility (also known as gliding motility), single cells move at the colony  
118 periphery, exploring their environment for food. Unlike S-motility, A-motility is not  
119 T4aP dependent but, instead, involves a motility machinery named Agl-Glt. This  
120 protein complex assembles at the leading pole of the cell and traffics directionally  
121 toward the lagging cell pole, attaching to the substratum thus powering the

122 forward movement of the cell. Aglt-Glt disassembles when it reaches the lagging  
123 pole (Figure 2) [20,21].

124 Therefore, *M. xanthus* presents a front-rear polarity, with the leading pole  
125 corresponding to the pole where the T4aP and gliding motility apparatus  
126 assemble.

127

128 A striking feature of *M. xanthus* motility is the presence of periodic directional  
129 reversals, where cells switch direction by 180° due to the inversion of cell polarity  
130 and thus redirection of pili and Agl-Glt assembly to the opposite cell pole.  
131 Regulated reversals are essential for the formation of multicellular patterns, the  
132 formation of so-called rippling waves and fruiting bodies [17,22-25].

133

### 134 **MglA, MglB and RomR form a biochemical oscillator**

135

136 A reversal provokes the activation of the two *M. xanthus* motility machineries at  
137 the new leading pole which is orchestrated by the small Ras-like GTPase protein  
138 MglA. MglA binds to the leading pole in its active GTP-bound form and  
139 presumably recruits key proteins of each motility systems to be assembled /  
140 activated (the exact activation mechanisms are only partially characterized and  
141 not the topic of this review) [26-29]. The polarity of MglA is controlled by two  
142 protein complexes, the newly identified RomRX system (formed by two proteins,  
143 RomR and RomX) and MglB [26,29-31]. During reversals, the RomRX complex  
144 recruits MglA to the new leading pole, apparently acting as a Guanine nucleotide  
145 Exchange Factor (GEF) and thus allowing MglA-GTP to bind polar effectors of  
146 the motility complexes [30]. On the other hand, binding to the lagging pole is  
147 prevented by MglB, a GTPase activating protein present at the opposite pole that  
148 converts MglA-GTP to the inactive GDP-bound state. MglA-GDP is diffuse in the  
149 cytoplasm and cannot interact with the poles [20]. Thus, MglA, RomRX and MglB  
150 define a polarity axis that controls the direction of movement. During reversals,  
151 MglA relocates to the opposite pole, switching the polarity axis, and allowing the  
152 cells to move in the opposite direction. As further discussed below, this switch  
153 operates due to the combined action of oscillating RomRX and signal  
154 transduction (Figure 3A and B).

155

156 Following a reversal and the targeting of MglA-GTP to the new leading pole (and  
157 hence activation of motility from this pole), RomRX slowly dissociates from the  
158 pole and accumulates at the lagging pole as RomR also appears to directly  
159 interact with MglB [30-32]. Remarkably, this gradual accumulation is driven by  
160 the slow dissociation of RomR, which acts as a slow pendulum for the oscillation  
161 and thus defines a typical relaxation step for the system (Figure 3A and B) [33].  
162 The dynamics of RomR does not appear to be regulated by signal transduction  
163 and operates at the same rate, independent of the genetic background or the  
164 environmental conditions. The system reaches steady state when RomRX  
165 molecules are fully relocated to the lagging pole, ready to recruit MglA-GTP at  
166 this pole. However and most importantly, MglA-GTP cannot readily relocate to  
167 this pole, likely because the GAP activity of MglB predominates and must be

168 inhibited for MglA to be recruited effectively by RomRX. In this situation, the  
169 GATE is closed and its opening requires a signal, which is provided by the so-  
170 called Frz system.

171

### 172 **The Frz system activates the polarity switch**

173

174 The Frz chemosensory pathway is essential to trigger the polarity switch. Frz  
175 mutants are perfectly motile but are unable to reverse and consequently are  
176 blocked in rippling and fruiting body formation. The Frz system is constituted of a  
177 chemosensory-like apparatus, centrally formed by a receptor-type methyl  
178 accepting protein (FrzCD) and a cognate CheA-type histidine kinase (FrzE)  
179 [20,32,34-39]. The connection between Frz and MglA has long remained unclear  
180 but recently, two direct FrzE-substrate response regulators (named FrzX and  
181 FrzZ) have been shown to interact with the MglAB polarity complex [33]. FrzX  
182 acts as a phosphorylation-dependent trigger: when phosphorylated by FrzE, it  
183 binds at the lagging pole, where it has been proposed to antagonize the action of  
184 MglB [33]. Thus, the action of FrzX opens the GATE, allowing RomRX to recruit  
185 MglA to the new leading pole and provoke a reversal (Figure 3A and B).

186

187 Reversals thus require that two threshold concentrations are reached at the  
188 lagging cell pole: [RomRX] allows efficient recruitment of MglA-GTP when MglB  
189 is efficiently antagonized by [FrzX~P]. Controlling reversals this way combines  
190 the advantages of a switch and an oscillator: the RomR relaxation step causes  
191 the polarity apparatus to naturally reverse poles, whereas a gating mechanism  
192 uncouples the dynamics of RomR and the reversal switch. It follows, that at low  
193 Frz signaling levels (*ie* when environmental signals are not present), the cell is  
194 therefore in a poised state, fully primed for reversal and the system can rapidly  
195 switch as soon as FrzX~P levels increase due to signal activation. Remarkably,  
196 at high Frz signaling levels (*ie* when environmental signals are persistent),  
197 FrzX~P is in excess and the dynamics of RomR become limiting. Given that the  
198 dynamics of RomR are highly regular, the system oscillates as a typical  
199 relaxation oscillator in this regime (Figure 3A and B). Thus, the genetic  
200 architecture of the Frz-Mgl system allows highly adjustable responses, poised  
201 and excitable or oscillatory, depending on environmental stimulations [33].

202

### 203 **FrzZ modulates the relaxation period**

204

205 The relaxation property of RomR also implies that FrzX~P-dependent stimulation  
206 is only possible if sufficient amount of RomR has accumulated at the lagging  
207 pole, which times a so-called refractory period during which no new reversal can  
208 be activated [33]. However, the relocalization of RomR is a slow process  
209 (minutes), greatly limiting the maximum reversal frequency. The FrzZ response  
210 regulator acts to limit the length of this refractory period by lowering the amount  
211 of RomR necessary at the lagging cell pole. How precisely FrzZ performs this  
212 function is unknown, but it can bind to the leading cell pole when phosphorylated  
213 and mathematical simulations suggest that FrzZ could accelerate MglA

214 dissociation from the leading cell pole [33,40]. Thus, FrzZ acts as a rheostat,  
215 tuning the refractory period in a phosphorylation-dependent manner and allowing  
216 fast reversal frequencies at high signal concentrations despite the slow dynamics  
217 of RomR (Figure 3A and B).

218

### 219 **Molecular mechanism of the polarity switch**

220

221 The exact molecular sequence of events that lead to Frz activation of the polarity  
222 switch remains to be determined. At the lagging cell pole, the accumulation of  
223 both RomRX and MglB lead to antagonizing GAP and GEF activities. However,  
224 no accumulation of MglA is observed until FrzX accumulates at the lagging cell  
225 pole in an MglB-dependent manner. Thus, FrzX~P could directly shift the balance  
226 between GAP and GEF activities in favor of the GEF and thus allow MglA to  
227 relocalize to the lagging cell pole (Figure 4). Consistent with this, MglA and MglB  
228 co-localize at the lagging cell pole for up to 30 s when the switch is provoked,  
229 suggesting that during this time window, the GAP activity of MglB is no-longer  
230 efficient [33]. The mechanism by which MglB is then relocalized to the opposite  
231 cell pole is not yet clear. Guzzo *et al.* [33] postulated that MglA induces the  
232 detachment of MglB, which then interacts cooperatively with itself and the  
233 membrane at the opposite pole. While this scenario is plausible, there is currently  
234 no evidence to support it and alternative mechanisms are possible. Other  
235 proteins could be involved as well, for example the MglB-like protein MglC and  
236 the PilZ-like protein PlpA [20,41,42]. The exact function of these proteins in the  
237 switch mechanism remains, however, mysterious. In particular, similar to MglB,  
238 PlpA is essential for MglA polarity and cells bearing a *p/pA* deletion reverse like  
239 the *mgIB* deletion mutant [42]. Thus, PlpA and MglB might function in the same  
240 molecular pathway, which will require further investigation in the future. (Figure 4)

241

242 The mechanism by which MglA detaches from the leading cell pole is also  
243 intriguing. While it has been proposed that RomR acts as a localization factor for  
244 MglA, MglA remains stably anchored at the leading cell pole even when the most  
245 of the RomR pool has relocalized to the lagging cell pole [32]. This apparent  
246 conundrum could be explained if following its activation, MglA-GTP interacts with  
247 other polar proteins, *ie* A- and S-motility effector proteins. However, it remains to  
248 be established how MglA-GTP detaches from the leading pole at the time of  
249 reversals; FrzZ~P likely participates in this mechanism, but it cannot be the sole  
250 mechanism given that cells still reverse (albeit at lower frequencies) in a *frzZ*  
251 mutant [33,43].

252



253 **Conclusion remarks**

254

255 In this review, we describe how a complex biochemical oscillator regulates *M.*  
256 *xanthus* polarity switch and its direction of movement. Because the *Myxococcus*  
257 polarity system incorporates a checkpoint into an oscillator, it allows excitable or  
258 oscillatory behaviors, depending on the stimulation intensity [33]. This design  
259 allows unique developmental transitions as mutants that cannot enter fast  
260 oscillations (*ie* the *frzZ* mutant) are unable to form fruiting bodies, and mutants  
261 that cannot escape from oscillations are incapable to form motility swarms  
262 [43,44]. In the future, it will be important to determine where and when motility  
263 oscillations are exactly required during the predatory lifecycle. The molecular  
264 signals that activate the Frz pathway remain unidentified which largely  
265 complicates this analysis. Remarkably, the Frz receptor-kinase complex is not  
266 assembled in the bacterial inner membrane, as most receptors do, but it localizes  
267 to the cytoplasm, interacting directly with the nucleoid [45]. The cognate  
268 response regulators (FrzX and FrzZ) thus act as diffusible messengers between  
269 the bacterial chromosome and the cell poles. Thus, it is possible that rather than  
270 sensing extracellular cues, the Frz complex senses drastic intracellular  
271 transitions (*ie* metabolic) and changes as a function of global physiology. Direct  
272 coupling with the bacterial chromosome could also couple Frz (and thus cell  
273 polarity) directly with the cell cycle, potentially linking cell growth to pattern  
274 formation. In the future, it will be essential to link molecular studies in single cells  
275 to large scale pattern formation to elucidate how these regulations lead to  
276 remarkable self-organization properties.

277

278 From a broader perspective, the Frz-Mgl network likely evolved from the co-  
279 option of a bacterial chemosensory-type system (Frz) to a Ras-like polarity  
280 complex (MglA) [35]. As a result, a biochemical oscillator became tuned by a  
281 signal transduction. Given that these functional modules are broadly conserved,  
282 it is possible that similar regulations might occur in other rhythmic biological  
283 systems, converting linear regulations into oscillations (and vice-versa) as a  
284 function of stimulation intensity. Hence, the layout of the *Myxococcus* regulatory  
285 network could be used as a framework to facilitate the elucidation of the  
286 properties and evolution of tunable biological oscillators.

287

288

289 **Figure legends**

290

291 **Figure 1:** Spatial oscillators control the positioning of cellular structures in  
292 bacteria.

293 A) The *E. coli* Min system positions the septal FtsZ ring at mid-cell. Pole-to-pole  
294 oscillations of MinCD ensures that the concentration of the MinC FtsZ inhibitor is  
295 minimal at mid-cell, allowing FtsZ tubulin polymerization at this site only.

296 B) McdB-driven intracellular oscillations of McdA position bacterial carboxysomes  
297 along the nucleoid, which here functions as a subcellular scaffold for organelle  
298 assembly.

299

300

301 **Figure 2:** Motility systems in *Myxococcus xanthus*.

302 MglA activates two motility systems at the bacterial cell pole. The S-motility  
303 system (otherwise known as twitching motility) is involved in the movement of  
304 cells in groups and involves retractile Type-IV pili that pull cells forward like  
305 grappling hooks. The A-motility system (otherwise known as gliding motility)  
306 requires the Agl-Glt complex that assembles at the leading cell pole and moves  
307 directionally toward the lagging cell pole. Propulsion is produced when moving  
308 complexes adhere to the underlying surface. Active Agl-Glt complexes are  
309 disassembled by MglB.

310

311

312 **Figure 3:** A gated relaxation oscillator controls cell polarity switch in *M. xanthus*.

313 A) Before a reversal, MglA-GTP is localized at the leading pole. MglB and  
314 RomRX localize to the lagging cell pole. The cell does not reverse because the  
315 GATE is closed. When FrzE becomes active, FrzX~P accumulates at the lagging  
316 cell pole and opens the GATE. The RomRX GEF complex then recruit MglA to  
317 the new leading pole and provoke a reversal. Following the reversal, RomRX  
318 slowly dissociates from the pole and accumulates at the lagging pole interacting  
319 directly with MglB. This slow process defines the relaxation step for the system  
320 and introduces a refractory period during which no new reversal can be  
321 activated. FrzZ~P, which also accumulates when FrzE is active, acts to limit the  
322 length of this refractory period set by RomR.

323 B) Simulated profiles of MglA, MglB, RomR and FrzX~P during the reversal cycle  
324 (adapted from Guzzo *et al.* [33]). Note that the simulation show that reversals  
325 only occur when requirements for both RomR and FrzX~P are fulfilled at the  
326 lagging cell pole. Therefore, if the [FrzX~P] is limiting the cell is primed and in an  
327 excitable state. On the contrary, if [FrzX~P] is high the slow dynamics of RomR  
328 set the reversal period and the cell oscillates. The dashed lines indicate the time  
329 of parity of the MglB levels.

330

331

332 **Figure 4:** Molecular model of the polarity switch.

333 Upon activation, nucleoid-bound Frz receptor-kinase complexes phosphorylate  
334 the two diffusible response regulators FrzX and FrzZ that localize to opposite

335 poles in their phosphorylated form. FrzX~P might directly inhibit the MglB GAP  
336 activity, while FrzZ~P might dissociate MglA from the pole and limit the length of  
337 this refractory period set by RomR. In absence of antagonizing GAP, the RomRX  
338 complex can recruit MglA-GTP at the lagging pole. The mechanism that leads to  
339 the relocalization of MglB is not clear and could require the action of other polar  
340 factors such as MglC and PlpA.  
341  
342  
343

344

345

346 **Conflict of interest statement**

347 Nothing to declare

348

349 **Acknowledgements**

350 TM is funded by an ANR Bactocompass (ANR-15-CE13-0006)

351

352

353

354 **References and recommended reading**

355

356 Papers of particular interest, published within the period of review, have been  
357 highlighted as:

358 \*of special interest

359 \*\*of outstanding interest

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377 polarity and cells bearing a *plpA* deletion reverse like a *mglB* deletion mutant,  
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399

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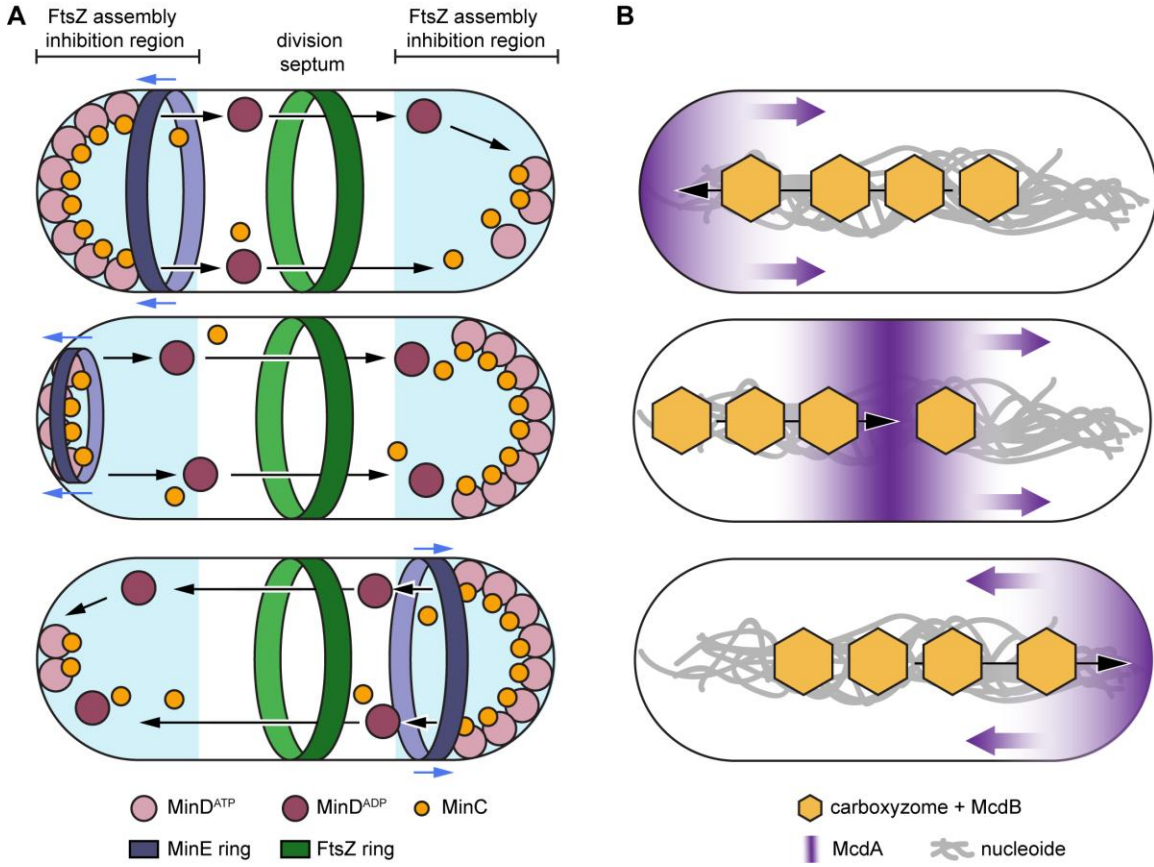
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Figure 1

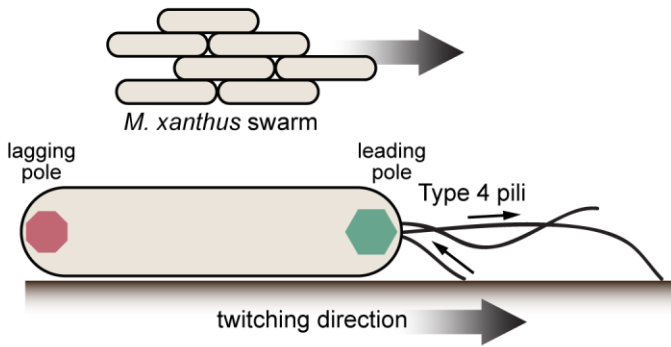


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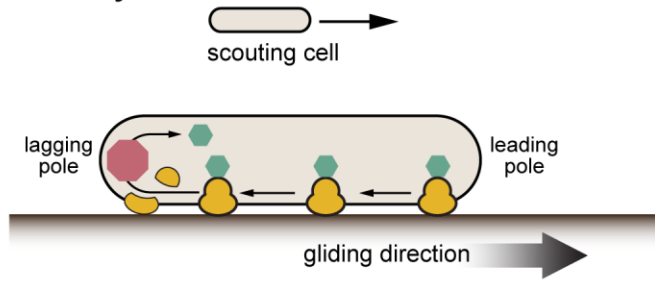
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Figure 2

**S-motility**



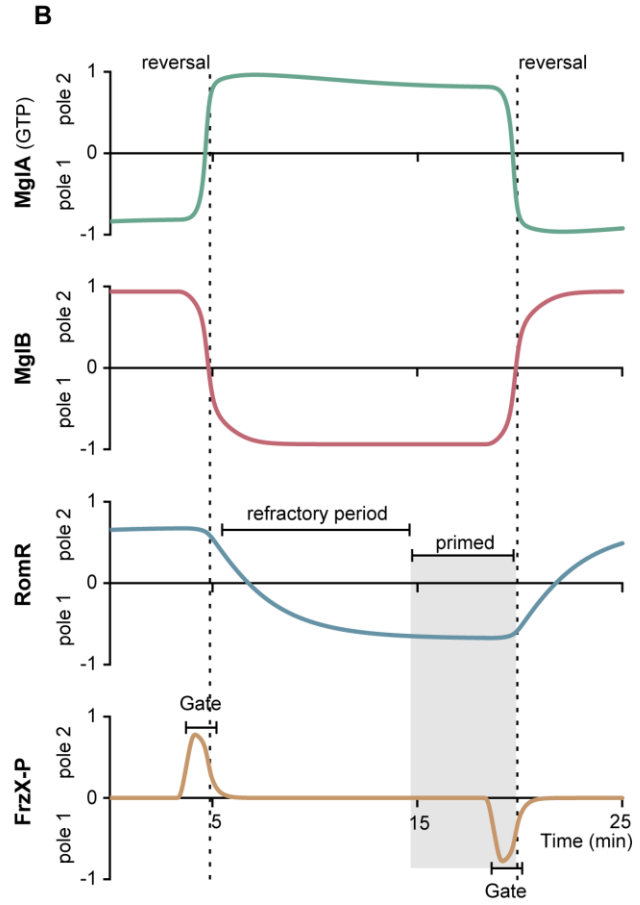
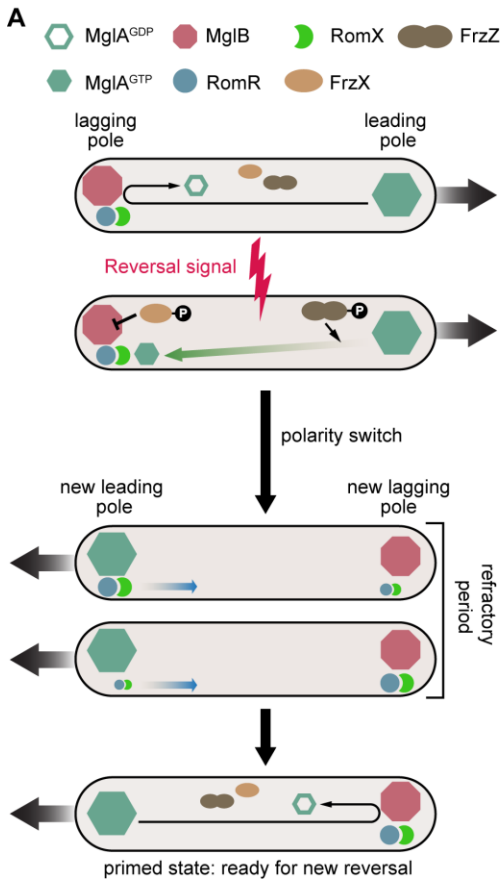
**A-motility**



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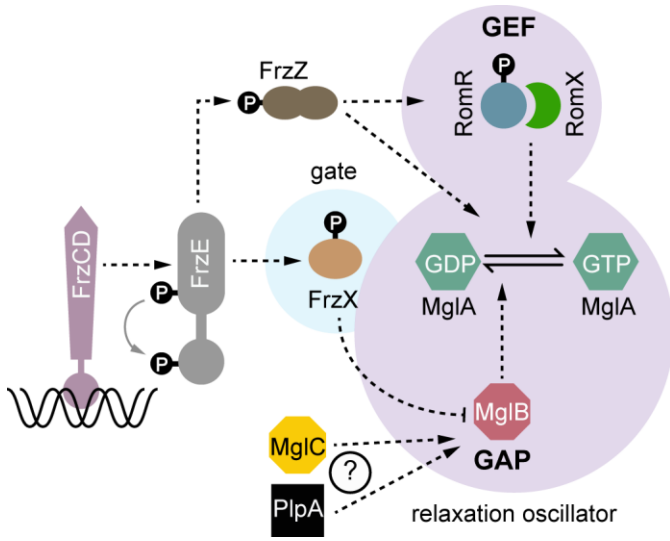
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