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

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Julien Herrou¹, Tâm Mignot¹

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¹Laboratoire de Chimie Bactérienne, CNRS - Aix Marseille University UMR 7283,
Institut de Microbiologie de la Méditerranée, Marseille, France.

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e-mails: tmignot@imm.cnrs.fr, jherrou@imm.cnrs.fr

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polarity, motility

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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
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346 **Conflict of interest statement**

347 Nothing to declare

348

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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,
378 suggesting that PlpA and MglB function in the same molecular pathway.

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397 pattern emerging from interactions among the Min proteins and with the
398 cytoplasmic membrane.

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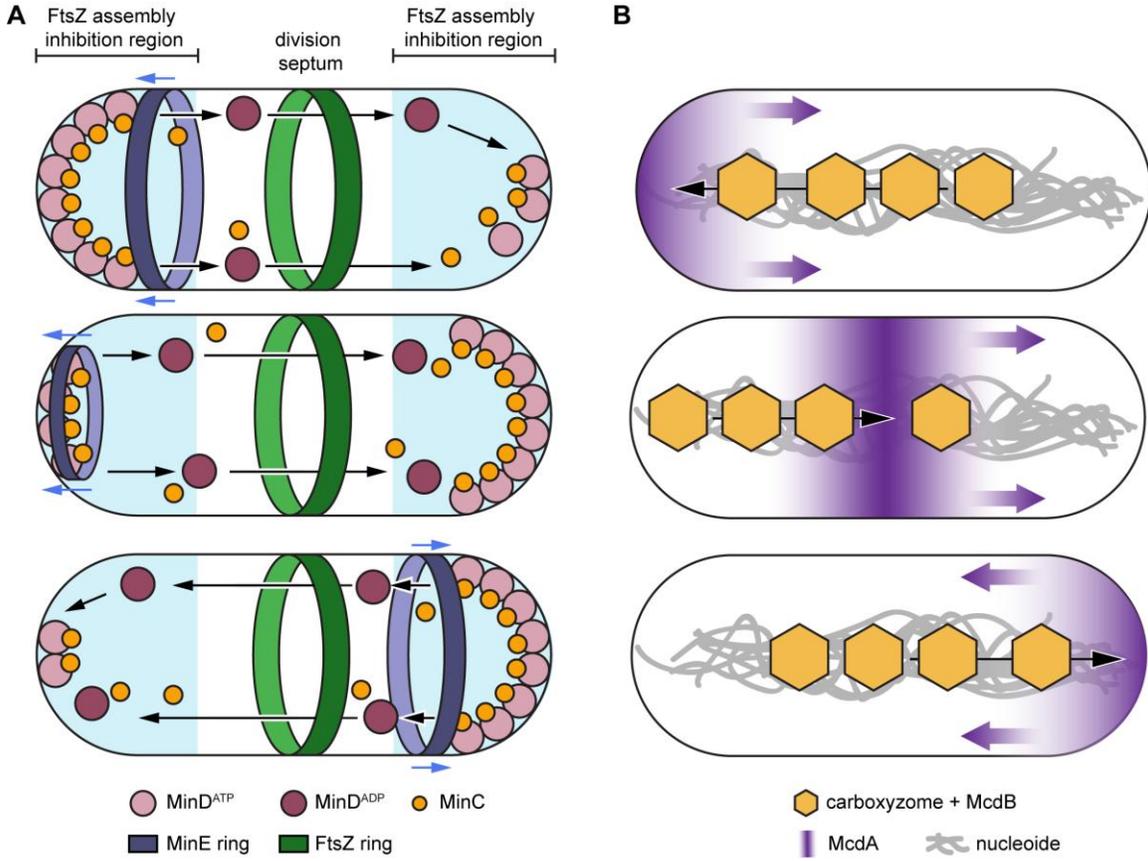
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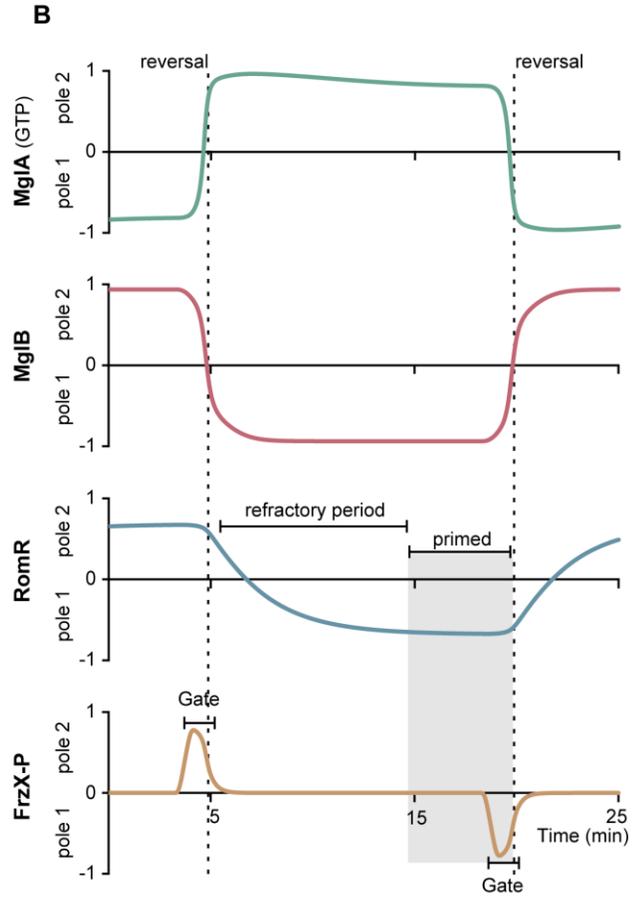
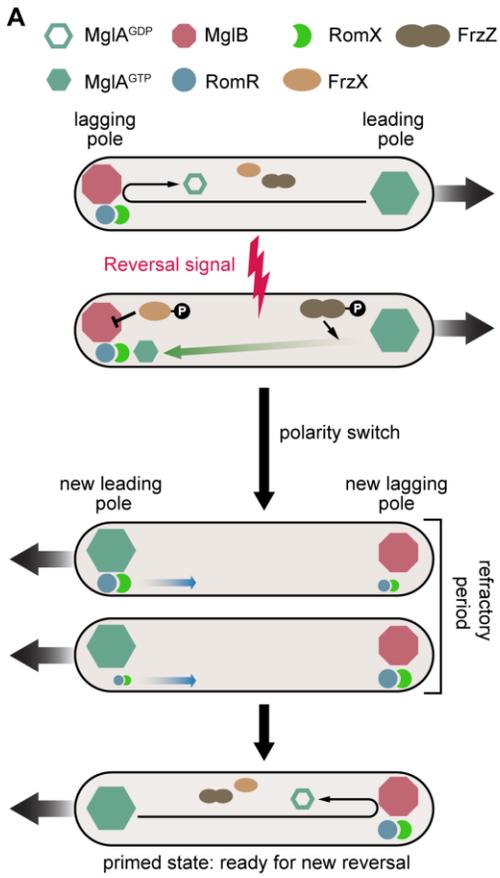
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Figure 1



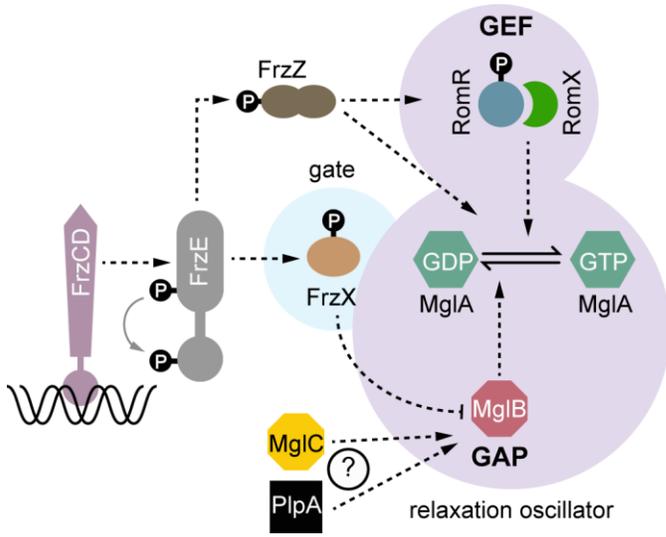
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546 Figure 3
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