1 **The common chromosomal periodicity of transcriptomes is correlated**
2 **with the bacterial growth rate**

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Abstract

The growth rate, representing the fitness of a bacterial population, is determined by the whole transcriptome. Chromosomal periodicity is a representative overall feature of the whole transcriptome; however, whether and how it is associated with the bacterial growth rate are unknown. To address these questions, we analyzed a total of 213 transcriptomes of genetically differentiated *Escherichia coli* strains growing in an assortment of culture conditions varying in terms of temperature, nutrition level and osmotic pressure. Intriguingly, the Fourier transform identified a common chromosomal periodicity of transcriptomes, which was independent of the variation in genomes and environments. In addition, fitting of the theoretical model found that the amplitudes of the periodic transcriptomes were significantly correlated with the growth rates. This novel finding successfully identified a single parameter representing the global pattern of the whole transcriptome for the first time and indicated that bacterial growth was correlated with the magnitude of chromosomal differentiation in gene expression. These results provided an alternative global parameter for evaluating the adaptiveness of a growing bacterial population and provided a quantitative rule that makes it possible to predict the growth dynamics according to the gene expression pattern.

Keywords: chromosomal periodicity, transcriptome, growth rate, population fitness

29 Introduction

30 The growth rate in the exponentially growing phase is the most important parameter
 31 representing both genetic and environmental influences on bacterial growth dynamics.
 32 Predicting the growth rate of a growing bacterial population according to the intrinsic
 33 status and/or extrinsic conditions is highly desirable. To date, extensive studies
 34 involving the systematic quantitative investigation of bacterial growth have been
 35 performed. By using systematic genetic constructs, e.g., single-gene knockout¹ and
 36 genome reduction,^{2,3} the contributions of both single genes and large genomic
 37 fragments to bacterial growth were quantitatively evaluated⁴⁻⁶. The finding of a
 38 correlation between the genome and the growth rate strongly suggests that population
 39 fitness is linked to genome-wide features in vivo^{5,7}.

40 The transcriptome, which illustrates a global view of the transcriptional abundance of
 41 all the genes distributed in the genome, is reorganized constantly in response to genomic
 42 and environmental perturbations⁸⁻¹⁰. As the transcriptome is known to be associated
 43 with population fitness¹¹⁻¹³, the contribution of the transcriptome to population fitness
 44 is of great interest. Our previous studies reported the coordination of gene expression
 45 with the growth rate¹³ and the linkage between transcriptome reorganization and
 46 increases in fitness in adaptation and evolution^{14,15}. These findings indicated that the
 47 whole transcriptome, rather than the specific regulation of limited gene groups,
 48 increased population fitness. Whether and how the whole transcriptome is linked to
 49 population fitness remains unknown.

50 A single parameter representing the whole transcriptome is critical for determining
 51 the linkage if it exists. Previous studies successfully demonstrated that the power law
 52 (Zipf's rule) was a universal principle governing the transcriptome in living organisms
 53^{16,17}; however, we failed to find the linkage between this law and the growth rate¹⁸. As
 54 an alternative global feature representing the transcriptome, chromosomal periodicity
 55 has been proposed^{19,20}, which is determined using the Fourier transform, a
 56 mathematical method used to estimate the periodic patterns in an entire dataset
 57 according to the sinusoidal wave²¹. Computational analyses identified some particular
 58 periods associated with bacterial transcriptomes^{19,20}, which were supported by the
 59 molecular functions and/or mechanisms related to the chromosomal topology²²⁻²⁴.
 60 These findings of chromosomal periodicity were used to obtain static snapshots of the
 61 whole transcriptome, and whether and how the chromosomal periodicity of the
 62 transcriptome is linked to the growth rate are under investigation.

63 In the present study, a total of 213 growth profile-associated transcriptomes were
 64 analyzed that represent an assortment of genetically differentiated *E. coli* cells growing

under or responding to various environments. This study seeks to determine whether the chromosomal periodicity of the transcriptome is robust or plastic in response to environmental and genetic differentiation and whether and how chromosomal periodicity is coordinated with bacterial growth.

Materials and Methods

E. coli strains and growth conditions

Three types of *E. coli* genomes were included in the transcriptome analyses: the full-length genomes of MG1655 and DH1 and the partial genome of MDS42². A number of genetically engineered strains were comprised of genomes of types DH1^{14,25} and MDS42¹³, which led to a total of 20 different genomic backgrounds. The growth media were all based on the minimal medium M63²⁶; if required, the medium was supplemented with factors, including amino acids, to compensate for the interruption of gene function resulting from genetic engineering. In addition, the growth temperature was also varied. Nine different media and seven different temperatures were used, which resulted in a total of 16 different environmental conditions. The *E. coli* growth status was evaluated in the exponential growth phase and the stress response phase. Only the transcriptomes associated with the exponential growth phase were linked with precise growth rates (165 transcriptomes) and were subjected to correlation analysis. The details of the genomic backgrounds and the environmental conditions can be found in previous reports^{13-15,18,25,27,28}.

Transcriptomes

The transcriptomes used in the present study were acquired from microarray raw data sets assigned the GEO access numbers of GSE33212, GSE49296, GSE55719, GSE52770 and GSE61749 by using the customized platform EcFS²⁹. The finite hybridization model³⁰ was applied to determine the gene expression levels, which were calculated as the log-scale mRNA concentrations (pM). Data filtering, normalization and averaging of the biological replicates for the subsequent transcriptome analyses were described previously. The resulting transcriptomes were associated with the growth profiles, genomic backgrounds and environmental conditions. The details were previously described in the corresponding studies^{13-15,25,27}. A total of 213 transcriptomes, comprising 72 combinations (biological repetition, N=2~7) that varied in terms of the genomic background and environmental conditions as described above, were included in the analyses.

101 *Computational analyses*

102 All computational analyses were performed with R ³¹. The gene expression levels on
103 a logarithmic scale were used for the analyses as described previously ^{18,32}. A total of
104 165 transcriptomes representing the exponential growth phase associated with the
105 repeated growth assay were subjected to correlation analysis of the growth rate (**r**) and
106 the periodic parameters (**a**, **b** and **c**). This resulted in 42 combinations of genomic and
107 environmental variations. The statistical significance of the Pearson correlation
108 coefficients was evaluated by the t-test. The Z-score was used for the standardization of
109 the MG1655 transcriptomes obtained from the present data sets and the GyrA Chip-seq
110 data for MG1655 obtained from another study ²⁰. The Z-scores of both the gene
111 expression and the GyrA binding activity were calculated and were averaged with a
112 sliding distance of 1 kb for the correlation analysis and the Fourier transform.

114 *Evaluation of chromosomal periodicity*

115 A standard Fourier transform was employed to determine the chromosomal periodicity
116 of the transcriptomes and the GyrA binding activity by using the periodogram function
117 in R. All 213 transcriptomes were subjected to the Fourier transform, in which the
118 expression data for 4393, 3760 and 4377 genes in the *E. coli* strains with the genomic
119 backgrounds of MG1655, MDS42 and DH1 were used, respectively. The CDS
120 information for MG1655, MDS42 and DH1 were obtained from the DDBJ databanks
121 under the accession IDs U00096, AP012306 and AP012030, respectively. The sizes of
122 the genomes used for the Fourier transform were 4642, 3976 and 4622 kb and
123 corresponded to the genomic backgrounds of MG1655, MDS42 and DH1, respectively.
124 The chromosomal periodicities of both the transcriptomes and the GyrA binding activity
125 were evaluated with a sliding distance of 1 kb and are shown in 100-kb bins. The
126 approximate curves of the periodicity were calculated using the highest peak of the
127 periodogram and were fitted by minimizing the square error of the approximate curve
128 and the series of expression values. The statistical significance of the periodicity was
129 assessed with Fisher's g test ²¹, which was performed using the GeneCycle package in
130 R.

132 **Results and Discussion**

133 *The common chromosomal periodicity of the transcriptome*

134 To investigate whether the growth conditions and the genomic background influenced
135 the chromosomal periodicity of the transcriptome, a total of 213 *E. coli* transcriptome
136 data sets, which were associated with the growth profiles and were acquired with the

137 same microarray platform, were used in the present study. The growth conditions were
138 varied in terms of temperature, nutrition level and osmotic pressure, and there was a
139 large variation in the genomic backgrounds (as described in the Materials and Methods).
140 Chromosomal fluctuations in gene expression were confirmed (Fig. 1A), and
141 chromosomal periodicity was evaluated with the Fourier transform.

142 Intriguingly, the analysis results showed the high level of common chromosomal
143 periodicity of the transcriptomes, which was independent of the growth conditions and
144 the genomic backgrounds. For instance, the most significant spectral powers (*i.e.*, the
145 max peak) identified in two transcriptomes associated with different growth rates (**r**)
146 were exactly the same (Fig. 1B, left panels). Consequently, this resulted in an identical
147 chromosomal periodicity (Fig. 1B, right panels), although the two transcriptomes
148 represented the *E. coli* cells growing at different temperatures. Overall, 202 out of 213
149 transcriptomes presented a universal chromosomal periodicity of six periods (Fig. 1C)
150 as the highest priority in the Fourier transform. Of note, all 11 exceptions showed a
151 chromosomal periodicity of six periods as the second priority. As the statistical
152 significance of the chromosomal periodicity was further proven by Fisher's g test for all
153 transcriptomes (Fig. S1), the determination of the common chromosomal periodicity of
154 transcriptomes, which consisted of six periods, was highly reliable. This result agreed
155 with those of previous studies reporting periodic transcriptomes either in wild-type *E.*
156 *coli* strains or under regular growth conditions^{20,27,33}.

157 In addition, the periodicity of the chromosomal dynamics of the transcriptomes was
158 somehow synchronized. Despite the large variation in both the genomic backgrounds of
159 the *E. coli* strains and the environmental conditions of the population growth, the six
160 periods of a total of 202 transcriptomes almost overlapped (Fig. 1D). The similar
161 directional changes in gene expression among the genomic positions further
162 demonstrated the universality of the chromosomal periodicity of the transcriptomes
163 irrespective of genetic and environmental disturbances. This was the first finding that
164 revealed that neither the number nor the wavelength of the periods was linked to
165 bacterial growth.

166

167 *Correlation between the growth rate and the amplitude of the periodic transcriptome*

168 Whether there was any parameter representative of the periodic transcriptomes linked to
169 bacterial growth was further investigated. The gene expression level, $Exp(x)$, was
170 related to the genome position (x) of the corresponding gene. The parameters affecting
171 the chromosomal periodicity of the transcriptome were theoretically defined in the
172 following formula (Eq. 1).

$$Exp(x) = a \times \sin\left(\frac{x+b}{T} \times 2\pi\right) + c \quad \text{Eq. 1}$$

Here, the parameters **a**, **b**, and **c** represented the amplitude of the period, the phase of the period (i.e., the genomic position of the period initiation), and the mean transcriptional level, respectively (Fig. 2A). The estimation of the three parameters was performed by minimizing the square error in the curve fitting. The constant **T** was the wavelength of the period of the highest spectral power estimated by the Fourier transform. A total of 165 transcriptomes, which represented the exponential growth phase and were associated with highly precise growth rates (**r**), were subjected to theoretical fitting with Eq. 1.

The theoretical fitting successfully identified a significant correlation between the growth rate and the amplitude of the periodic transcriptome. The values of **a**, **b** and **c** calculated by curve fitting were averaged among the biological repeats, which led to 42 combinations that varied in terms of the genomic background and/or environmental conditions. Note that parameter **b** was further normalized because of the variation in the genome length. The parameter **a** was positively correlated with the growth rate (Fig. 2B), whereas such a correlation was not detected for the parameters **b** and **c** (Fig. S2). The analysis clearly determined a simple correlation between the growth rate and the amplitude of the period, although the 165 transcriptomes with 42 combinations largely differed in terms of the genotypes and environments. This strongly suggested that population fitness was correlated with the magnitude of differential transcription along the chromosome.

Further investigations of the contributions of the genomic background and the environmental conditions failed to observe any significant relationship with the growth rate. According to previous reports^{13-15,18,25}, four types of environmental variations were roughly categorized as normal conditions and conditions with changes in temperature, nutrition level and osmotic pressure. The distributions of the four parameters representing the growth and the periodicity of the transcriptome were largely dissimilar among the four categories (Fig. 2C), which reflected the properties of the data sets. No environmentally dependent feature or correlation among the parameters **a**, **b**, and **c** was found (Fig. 2C). Additionally, genetic engineering might affect the phase of the period (i.e., normalized **b**), as a difference was detected between the wild-type genome and the other genomes (Fig. S3). The genetic reconstruction possibly interrupted the genomic position of the period initiation, although more datasets were required to support this assumption.

208 *Mechanisms of the universal chromosomal periodicity of transcriptomes*

209 To understand the universality of the periodicity of transcriptomes, a simple
210 assumption was made that the essential genes determined the six periods. However,
211 neither deleting the essential genes from the transcriptome data nor substituting the true
212 expression values with zero altered the common periodicity of the transcriptome (Fig.
213 S4). This result indicated that the periodicity of the transcriptome was not simply due to
214 the genomic localization of the essential genes, although it is unclear whether and how
215 the absence of the essential genes triggered the transcriptional changes of the
216 nonessential genes, as deleting the essential genes from the genome was impractical.

217 As the chromosomal structure might contribute to transcriptional activity^{32,34-36},
218 whether the common chromosomal periodicity of the transcriptome was attributed to the
219 chromosomal organization was determined. The macrodomain model was proposed for
220 the *E. coli* chromosome, with four structured domains and two nonstructural regions
221³⁷⁻⁴⁰. The normalized periodicity of the transcriptomes showed that the six periods were
222 roughly positioned within the six domain regions of the *E. coli* chromosome (Fig. 3A),
223 which was consistent with previous findings^{20,27,33}. The highly overlapping phases of
224 the periodic transcriptome (Fig. 3A) suggested that the chromosomal macrodomain
225 structure was robust against genomic and environmental disturbances.

226 Moreover, the molecular mechanism related to the DNA topology probably played a
227 role in determining the chromosomal periodicity of the transcriptome. Bacterial
228 chromosomal structures are highly dynamic and compacted in association with
229 nucleoid-associated proteins (NAPs). Previous studies indicated that the chromosomal
230 supercoiling of domains ~10 kb size^{20,22} was potentially attributed to the chromosomal
231 localization of nucleoid-associated proteins, *e.g.*, H-NS⁴¹, and that of domain 600~800
232 kb size might be triggered by DNA gyrase²⁰. As the common period identified in the
233 present study was ~700 kb, the participation of the subunit of the DNA gyrase, GyrA,
234 was confirmed. A highly significant correlation was verified between the transcriptome
235 of the wild-type strain MG1655 in the present study and the abundance of
236 chromosomally bound GyrA in a previous report²⁰ (Fig. 3B). Such a correlation seemed
237 to be common in all transcriptomes (Fig. S5) if the properties of the binding of GyrA to
238 the genome remained unchanged. The correlation between gene expression and binding
239 activity suggested the similarity of the chromosomal periodicity of GyrA binding and
240 that of the transcriptome. Although the six periods were not the first priority for GyrA
241 binding (Fig. S6), the chromosomal periodicities of GyrA binding activity and the
242 transcriptome in MG1655 were somehow coordinated (Fig. 3C).

243

244 *Linking the periodicity of the transcriptome to population fitness*

245 The present study successfully found a direct linkage between population dynamics
246 and the whole transcriptome (Fig. 4). The whole transcriptome is influenced by both the
247 genomic background and the environmental conditions; consequently, it determines
248 bacterial growth. Previous studies of transcriptomes successfully classified the genes
249 into diverse categories that functioned either specifically in response to environmental
250 changes or generally in relation to the growth rate¹¹⁻¹³. However, whether there was any
251 quantitative relationship directly linking the two global features of growth and the
252 transcriptome remained unaddressed.

253 The present study first identified a single parameter that represented well the global
254 features of the whole transcriptome. That is, the amplitude of the chromosomal
255 periodicity of the transcriptome represents the magnitude of the chromosomal
256 differentiation of gene expression. Moreover, fast growth was linked to a large
257 amplitude of the periodic transcriptome (Fig. 4, solid curves). The correlation between
258 the growth rates and the amplitudes of periodic transcriptomes was independent of the
259 environmental conditions and the genomic backgrounds. This novel finding was a
260 breakthrough for understanding how the whole transcriptome determined population
261 fitness because it was the first demonstration that the magnitude of chromosomal
262 differentiation of gene expression was correlated with the growth rate.

263 The growth rate was the only global parameter representing the adaptiveness of a
264 growing bacterial population. The amplitude of the periodic transcriptome could be
265 considered an alternative global parameter for evaluating population fitness. In addition
266 to network reconstruction⁴², the assessment of the global pattern of the whole
267 transcriptome might be applied for predicting population fitness, which would be
268 beneficial for industrial applications to substrate production and the fundamental
269 investigation of living principles.

271 **Acknowledgments**

272 We thank Shigeto Seno for the programming assistance. This work was supported by
273 the JSPS KAKENHI Grant-in-Aid for Scientific Research (B) (grant number 19H03215
274 (to BWY)).

276 **Competing interests**

277 The authors declare that there are no competing interests.

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398 **Figure legends**

399 **Figure 1 Chromosomal periodicity of the transcriptome. A.** All transcriptomes used
400 in the present study. The transcriptional levels of every 1 kb sliding window and 100 kb
401 smoothing are shown. The color variation indicates the transcriptomes of individual
402 strains. **B.** Periodograms of the transcriptomes. Two transcriptomes with different
403 growth rates are shown. The growth rates, r , are indicated in the insets. The left and
404 right panels represent the distributions of the Fourier-transformed periodic wavelengths
405 on a logarithmic scale and the estimated chromosomal periodicity of the transcriptome,
406 respectively. The broken lines and solid curves in red indicate the highest power spectra
407 (the max-peak) estimated by the Fourier transform and the corresponding fitted period
408 of the transcriptome, respectively. The transcriptional levels for every 1 kb sliding
409 window and 100 kb smoothing are shown. **C.** Distribution of the periods corresponding
410 to the max-peak. Orange and blue indicate the ratios of the six periods and the single
411 period among the 213 total transcriptomes, respectively. **D.** Overlapping periods of the
412 transcriptomes. The chromosomal periodicity of 202 transcriptomes showing six periods
413 (orange in **C**) were plotted together. The color variation corresponds to that shown in **A**.

414
415 **Figure 2 Correlation between the chromosomal periodicity and the growth rate. A.**
416 Illustration of the parameters defined for the periodic transcriptome. The parameters (**a**,
417 **b** and **c**) used in Eq. 1 are indicated. Black and red lines represent the transcriptome and
418 the fitted period, respectively. **B.** Scatter plot of the amplitude of the six periods and the
419 growth rate. The standard errors of the biological replicates are indicated. The
420 correlation coefficient and its significance are indicated. **C.** Relationships among the
421 parameters defined for the chromosomal periodicity and the growth rate. The
422 relationship between any two of **a**, **b**, **c** and r is shown in matrix form. Pink, blue, green
423 and purple represent the environmental variations in temperature, osmotic pressure, and
424 nutritional level and normal conditions, respectively.

425
426 **Figure 3. Comparison of the common periodicity of the transcriptomes to**
427 **chromosome structures. A.** Relationship between the chromosomal macrodomains and
428 the periodic transcriptomes. The normalized periodic transcriptomes are shown. Four
429 macrodomain regions and two nonstructural regions are shown in solid color and as
430 transparent, respectively. The macrodomains of the Ori, Right, Ter and Left regions are
431 shown in green, red, light and dark blue, respectively. **B.** Scatter plot of the
432 transcriptome versus GyrA binding activity in MG1655. Standardization of both the
433 mean expression levels and the GyrA Chip-seq data were performed by determining the

434 z-score. The correlation coefficients and the statistical significance are indicated. **C.**
 435 Comparison of the transcriptome and the GyrA binding activity of the wild-type
 436 genome MG1655. Red and black curves indicate GyrA binding activity and the
 437 transcriptome, respectively. Both were calculated using a 1 kb sliding window and are
 438 shown according to the 100-kb moving average.

439

440 **Figure 4 Scheme of the correlation between the growth rate and the chromosomal**
 441 **periodicity of the transcriptome.** Shadowed boxes indicate the profiles of the whole
 442 transcriptome and the corresponding population dynamics. The broken and solid curves
 443 in the upper box indicate the small and large amplitudes of the periodic transcriptomes,
 444 respectively, and those in the bottom box indicate slow and fast growth, respectively.

Figure 1

Figure 2

Figure 3

Figure 4