

1 **Liberation from equations: An equation-free method reveals the ecological interaction networks**
2 **within complex microbial ecosystems**

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18
19 **Abstract**

20 Mapping the network of ecological interactions is key to understanding the composition, stability,
21 function and dynamics of microbial communities. These ecosystem properties provide the
22 mechanistic basis for understanding and designing microbial treatments that attempt to promote
23 human health and provide environmental services. In recent years various approaches have been
24 used to reveal microbial interaction networks, inferred from metagenomic sequencing data using
25 time-series analysis, machine learning and statistical techniques. Despite these efforts it is still not
26 possible to capture details of the ecological interactions behind complex microbial dynamics. Here,
27 we develop the sparse S-map method (SSM), which generates a sparse interaction network from a
28 multivariate ecological time-series without presuming any mathematical formulation for the
29 underlying microbial processes. We show that this method outperforms a comparative equation-
30 based method and that the results were robust to the range of observational errors and quantity of
31 data that we tested. We then applied the method to the microbiome data of six mice and found that
32 the mice had similar interaction networks when they were middle- to old-aged (36-72 week-old),
33 characterized by the high connectivity of an unclassified Clostridiales. However, there was almost
34 no shared network patterns when they were young- to middle-aged (4-36 week-old). The results
35 shed light on the universality of microbial interactions during the lifelong dynamics of mouse gut-
36 microbiota. The complexity of microbial relationships impede detailed equation-based modeling, and
37 our method provides a powerful alternative framework to infer ecological interaction networks of
38 microbial communities in various environments.
39

40 **Introduction**

41 Microbial communities contribute to the evolutionary fitness of other living organisms by inhabiting
42 their bodies (Mueller and Sachs 2015) and surroundings (Panke-Buisse et al. 2015, Heederik and
43 von Mutius 2012, Chaparro et al. 2012). For example, the gut microbiota assists host metabolism
44 (Sommer and Bäckhed 2013, Tremaroli and Bäckhed 2012) and provides defense against pathogens
45 (Kamada et al. 2013). This understanding has motivated the development of microbial medicinal
46 interventions that attempt to treat various disorders through the manipulation and control of
47 microbial communities (Borody and Khoruts 2012). Furthermore, an emergent property of the
48 microbial community is the potential contribution to environmental remediation through the
49 degradation of pollutants (Iranzo et al. 2001, Swenson et al. 2000). The composition, stability,
50 function and dynamics of a microbial community provides the mechanistic basis for these microbial
51 treatments, and closer ties between these ecosystem properties and ecological interaction networks
52 (interaction webs) have been revealed (Tylianakis et al. 2010). Hence, an understanding of ecological
53 interaction networks is crucial for both human health and environmental sustainability. While it is
54 difficult to study complex microbial interactions using traditional laboratory cultivation approaches,
55 recent developments in next generation sequencing technology and high performance computing
56 environments have enabled various approaches for revealing ecological interaction networks,
57 ranging from time-series analysis, machine learning and statistical techniques (Vacher et al. 2016,
58 Faust et al. 2015, Bucci and Xavier 2014, Faust and Raes 2012). However, there are currently no
59 sufficiently effective methods for capturing details of ecological interactions within microbial
60 communities, which frequently exhibit complex dynamics (Gerber 2014, Ravel et al. 2013, Pepper
61 and Rosenfeld 2012, Relman 2012, Caporaso et al. 2011, Dethlefsen and Relman 2011).

62
63 An ecological interaction network is defined as a directed network that describes interactions
64 between organisms, such as mutualisms, competition and antagonistic (predator-prey) interactions
65 (Faust and Raes 2012, Morin 2009). An ecological interaction network is generally described as a
66 pairwise interaction matrix whose elements take zero, positive or negative values with regard to the
67 effect of one species on the other. Here, we summarize the ties between ecological interaction
68 networks and other ecosystem properties in three main points. First, the stability of an ecological
69 system relies on its ecological interaction network, as is known from the seminal work of May (1973)
70 that formulated how the stability of an ecological system relates to the density and strength of its
71 ecological interactions. In microbial communities in particular, mutualistic interactions may have a
72 disruptive effect on community stability (Coyte et al. 2015). Second, there are extensive studies
73 suggesting that an interaction network is crucial to the development and maintenance of microbial
74 ecosystem functions (reviewed by Vacher et al. 2016). For example, findings from a type of artificial
75 selection experiment led Blouin et al. (2015) to suggest that reducing interaction richness is crucial
76 to developing and maintaining microbial ecosystem function in terms of low CO₂ emission. Third, an
77 ecological interaction network can be used to identify key species having significant effects on the
78 stability and/or function of ecological systems out of proportion to their abundance (Jordan 2009,

79 Power et al. 1996, Paine 1969). For example, Jordan (1999) proposed a “keystone index” that
80 identifies key species based on their topological position within an interaction network, a-pioneering
81 theoretical development underpinning recent microbial community studies (Toju 2016, Berry and
82 Widder 2014).

83

84 An ecological *interaction* network is different from an ecological *association* network such as a
85 correlation network (Friedman and Alm 2012) or co-occurrence network (Faust et al. 2012).
86 Although correlations between time-series data are often used as a proxy for interactions between
87 species, this is not a reliable method even if a strong correlation exists between two species (Fisher
88 and Mehta 2014). A co-occurrence network only implies the presence of underlying ecological
89 interactions, whereas it provides significant information regarding associations between microbial
90 species (Vacher et al. 2016). As an alternative approach, algorithms have been developed to infer
91 ecological interaction networks directly from microbial time-series (Bucci et al. 2016, Fisher and
92 Mehta 2014, Jiang et al. 2013). However, these algorithms may not be applicable to the complex
93 dynamics of microbial communities, which require the following algorithm properties. First, a time-
94 series demonstrating non-equilibrium dynamics must be available because such dynamics are
95 common in microbial interaction networks. There are many reasons for this, such as species
96 interactions, environmental fluctuations, experimental perturbations, invasions and aging, and
97 understanding the dynamics resulting from these processes is clearly an important goal. Second, a
98 method that can capture microbial relationships without any presumption regarding their
99 mathematical formulation (in other words, an equation free approach) is desirable. As claimed for
100 ecological systems in general (Deyle et al. 2015), ecological interactions are often nonlinear, i.e., the
101 effect of species X on Y is not simply proportional to the abundance of Y, and attempting to
102 formulate all these relationships into mathematical functions is not realistic (Bashan et al. 2016,
103 DeAngelis and Yurek 2015). This fact will reduce the reliability of approaches that assume *a priori*
104 any underlying equation. Overcoming these obstacles will widen the applicability of network
105 inference methods without losing their reliability, and will promote our understanding on microbial
106 communities further.

107

108 We developed an algorithm, the Sparse S-Map method (SSM; Fig 1, see Materials and Methods),
109 that satisfies the above requirements. This algorithm generates a sparse interaction network from a
110 multivariate ecological time-series without assuming any particular underlying equation. Using
111 simulated multispecies population dynamics, we compared the performance of SSM to a comparable
112 equation-based method, sparse linear regression (SLR) to highlight the differences between
113 equation-free and equation-based methods. The robustness of the SSM’s performance against
114 observational error and dataset size was also tested. We then applied the SSM to the time-series of
115 gut-microbiota taken from the faeces of six mice over 72 weeks. To harness data limitations (18 time
116 points per mouse), we performed network inference by aggregating the data of five mice and
117 selected the network that best explained the dynamics of the remaining sixth mouse. This was also

118 a cross-validation test for the universality of ecological interaction networks among mice.

119

120 **Result**

121 *Sparse S-map method*

122 The sparse S-map method (SSM) is an algorithm that executes a forward stepwise regression
123 scheme with bootstrap aggregation (“bagging”) to calibrate species’ interaction topology, i.e. with
124 which species a focal species interacts, for S-map (Dixon et al. 1999, Sugihara et al. 1996, Sugihara
125 1994). In other words, the SSM is a data-oriented equation-free modelling approach (empirical
126 dynamic modelling; Deyle et al. 2015, Ye et al. 2015, Deyle et al. 2013, Sugihara et al. 2012) for
127 multispecies ecological dynamics whose interaction topology is unknown.

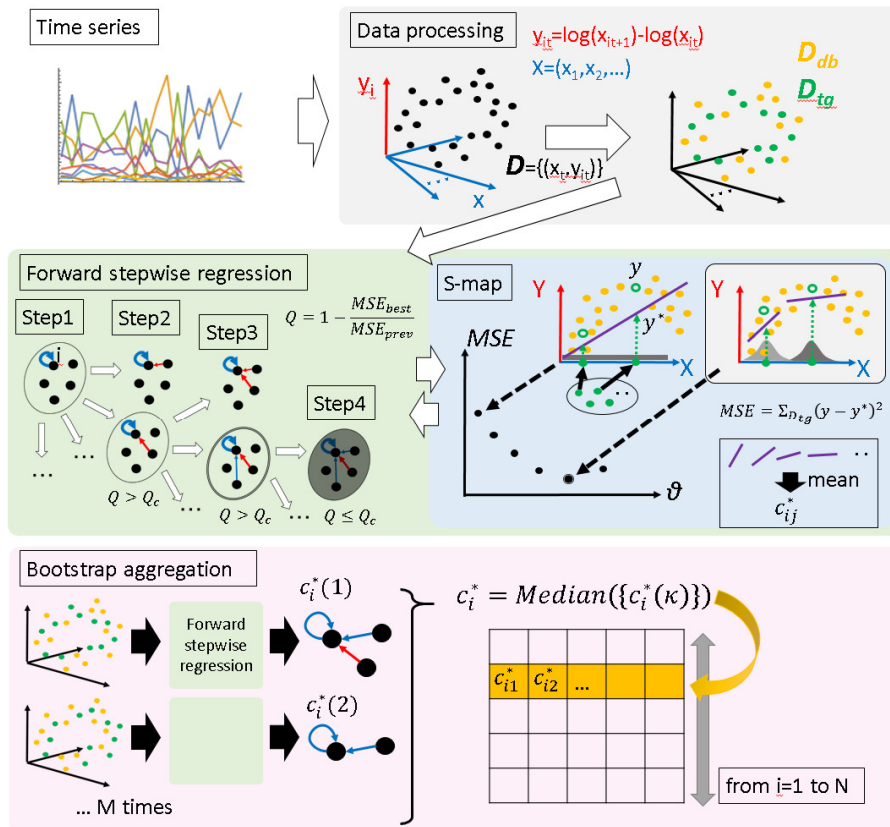
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129 S-map is a locally weighted linear regression model used for the mechanistic prediction of complex
130 ecological dynamics (Deyle et al. 2015). It is applicable to complex ecological dynamics without any
131 limitation in the dynamic property of given data and requires no special effort in formulating the
132 underlying species relationships into mathematical functions. However, so far it has only been
133 applicable to ecological systems with a small number of species whose interaction topology is
134 already known. By applying a forward stepwise regression with bootstrap aggregation, the SSM
135 realizes the appropriate selection of the interaction topology for S-map so that S-map becomes most
136 relevant for explaining a given set of data points. The ability of S-map to describe non-linear species
137 relationships makes the selection of interacting species reliable.

138

139 The SSM is essentially a non-parametric method that does not require any additional effort to
140 adjust parameters for the given data. Furthermore, owing to the forward stepwise scheme, it is
141 applicable to both absolute and relative abundance data without special treatment (Fisher and
142 Mehta 2014). Fisher and Mehta (2014) have already applied the forward stepwise scheme with
143 bagging to a linear regression model and thus developed an algorithm inferring the sparse
144 interaction matrix (sparse linear regression; SLR). However, because of the use of linear regression
145 model, the authors limited the applicability of SLR to systems whose dynamics are close to
146 equilibrium.

147



148

149 Figure 1. Overview of the sparse S-map method (SSM).

150

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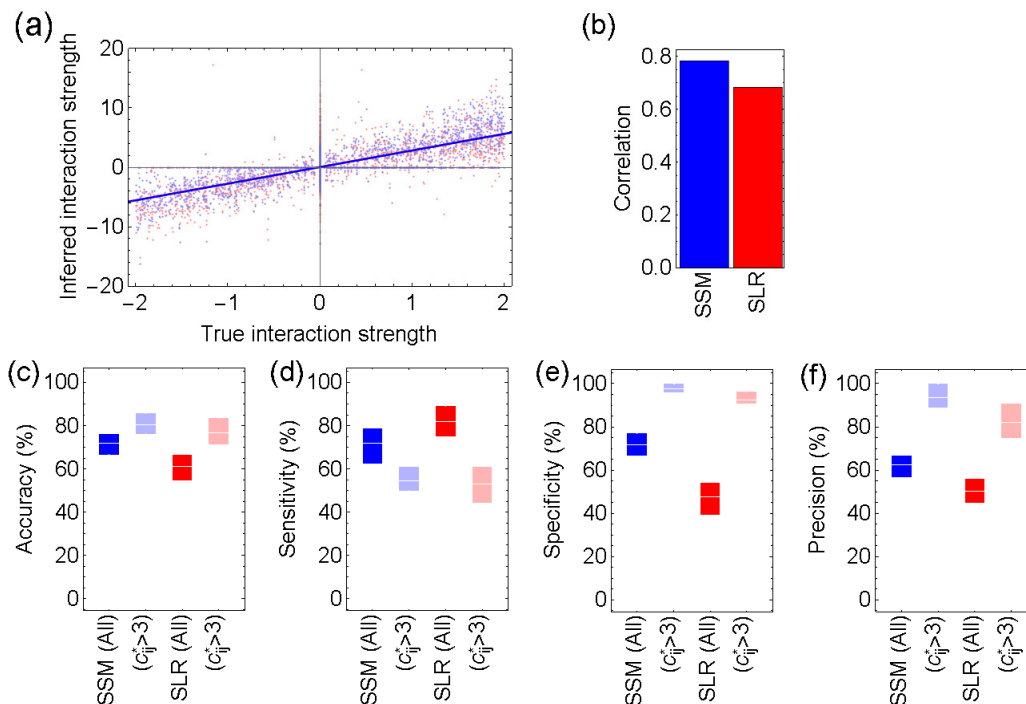
152 *Performance of the SSM*

153 To compare equation-free and comparative equation-based methods, we tested the performance of
 154 the SSM and SLR for complex ecological dynamics generated from a generalized Lotka-Volterra
 155 model with seven species with random interactions (see Materials and Methods). A significant
 156 positive correlation ($p < 0.01$) between inferred interaction strength and that of the true network
 157 was found in both the SSM and SLR, although the SSM showed a stronger correlation than SLR
 158 (Fig. 2ab). In both methods, the inferred strength was slightly greater than the actual interaction
 159 strength because of the non-linear species relationships. However, the correlation between actual
 160 and inferred interaction strengths assures their correspondence.

161

162 Two major performance criteria for network inference methods are sensitivity (the ratio of detected
 163 interacting species pairs with respect to all interacting pairs) and specificity (the ratio of detected
 164 non-interacting species pairs with respect to all non-interacting pairs). Furthermore, accuracy
 165 (sensitivity times the ratio of interacting pairs plus specificity times the ratio of non-interacting
 166 pairs) quantifies the overall performance of the method for discriminating interacting and non-
 167 interacting pairs. Figure 2c shows that the mean accuracy of the SSM was approximately 72%, 10%
 168 greater than that of SLR. The SSM had greater specificity than SLR, which compensated for its
 169 lower sensitivity. This means that the SSM is more conservative than SLR in finding a link between

170 two species, which makes the SSM accurate than SLR.
 171 Another important question is how reliable the detected interactions are. Hence, we also calculated
 172 precision (the ratio of detected interacting species pairs that actually interact with respect to all
 173 detected interacting pairs). The mean precision of the SSM was 62%, 10% greater than SLR. The
 174 SSM thus outperformed SLR in both accuracy and precision. However, 62% precision means that
 175 more than one third of the detected links are false. One remedy for this was obtained by introducing
 176 a threshold value for accepting inferred interactions. For example, when filtering out interactions
 177 whose inferred strength is less than three (approximately 40% of all detected interactions remain;
 178 Fig.S1), the mean precision of the SSM exceeded 90%, whereas it was approximately 80% in SLR.
 179

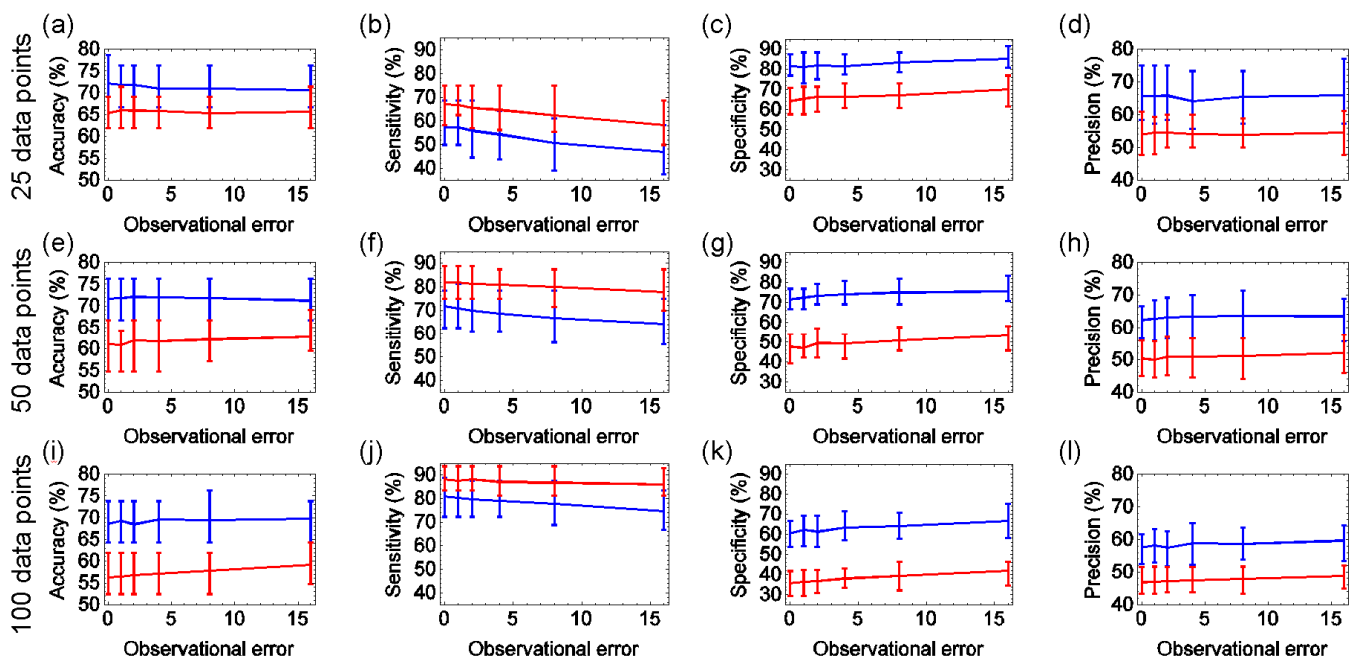


180
 181 Figure 2. Performance of the SSM and SLR for simulated ecological dynamics. Scatter plot with
 182 regression line (a), and correlation measured by Pearson's correlation coefficient (b). Points are
 183 assembled from 100 network inference results for time-series with 100 data points sampled from
 184 dynamics generated from a seven species GLV model with random species interactions. Accuracy (c),
 185 sensitivity (d), specificity (e) and precision (f), is calculated separately for each of 100 trials for the
 186 SSM and SLR, either including all interactions or after excluding inferred interactions whose
 187 strength is less than three. Bars indicate the first and third quartiles, and the line indicates the
 188 mean. All values are calculated after excluding intra-specific interactions.

189
 190
 191 *Robustness of the SSM for observational errors and data size*

192 Both mean accuracy and precision of the SSM outperformed SLR for all dataset sizes and
 193 observational errors that we tested (Fig. 3). The mean accuracy and precision was robust against
 194 increases in observational error because the increase in specificity compensated for the decrease in

195 sensitivity. The increase in dataset size from 25 to 100 points raised mean sensitivity by 20% in both
196 the SSM and SLR, while it reduced mean precision by 7%. More importantly, it reduced mean
197 accuracy by only 5% in the SSM but by 10% in SLR. Thus, increasing dataset size generally
198 enhances both methods to detect more links, while this benefits the SSM more than SLR because its
199 negative effect on accuracy is weaker in the SSM. The mean precision for inferred networks after
200 excluding weak (less than three) interactions was over 90% in the SSM for the all dataset sizes and
201 observational errors we tested (Fig.S2). In contrast to the cases when all interactions were
202 considered, no negative effect on accuracy or precision was found in both methods. It should be
203 noted that in figure 2S, among 100 trials, approximately 20% of the networks that were inferred
204 from 50 data points and that the 40% of those inferred from 25 data points were not included
205 because they had no inter-specific links.
206

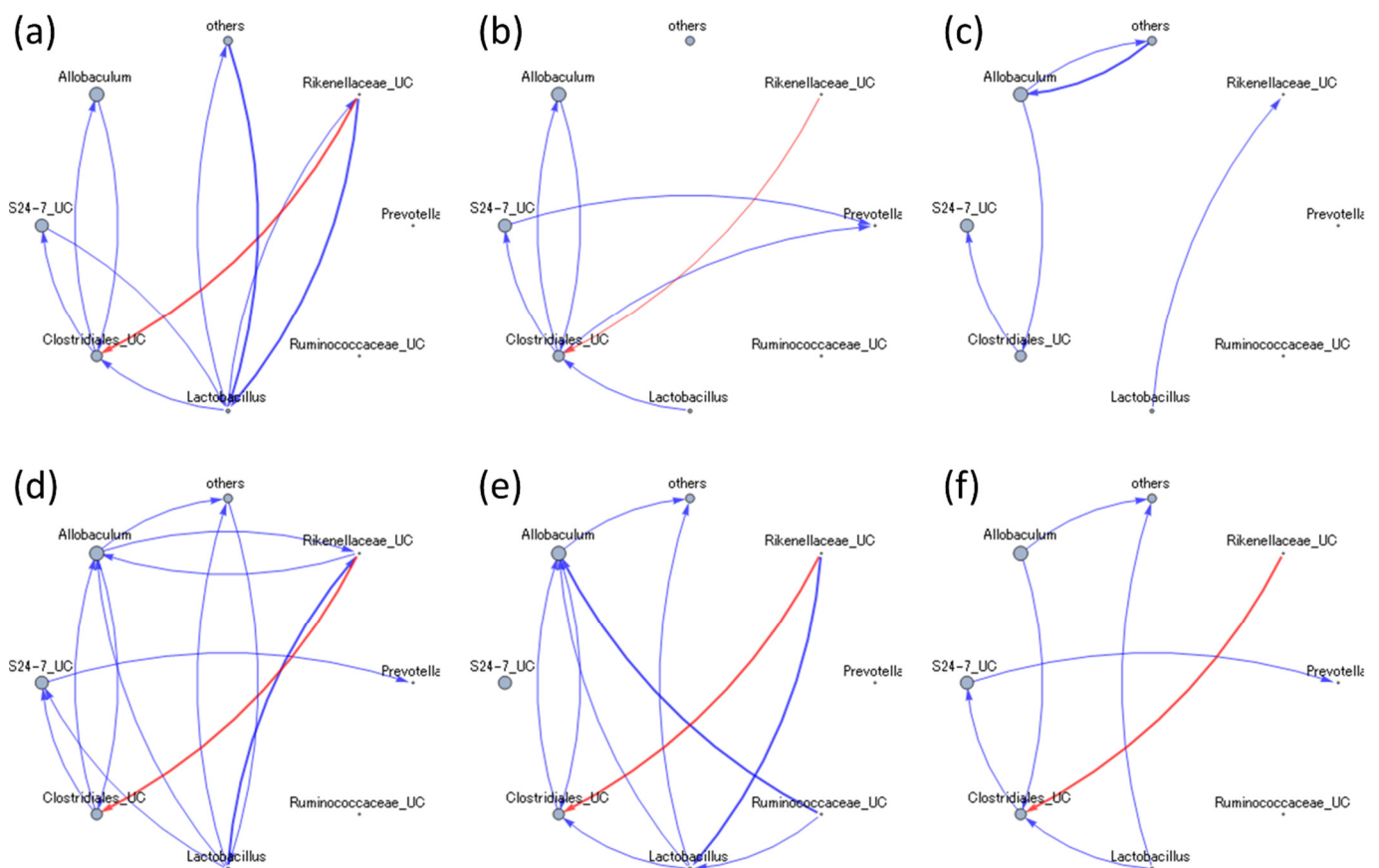


207
208 Figure 3. Robustness of the SSM and SLR for observational errors and data size. Accuracy,
209 sensitivity, specificity and precision for different observational errors were calculated for time-series
210 with 25 data points (a-d), 50 data points (e-h) and 100 data points (i-l) sampled from simulated
211 ecological dynamics. Blue lines indicate the SSM and red lines indicate SLR. Solid lines indicate the
212 mean value and the error bars indicate the first and the third quartiles. All results are calculated
213 from 100 different time-series generated from a seven species GLV model with random species
214 interactions. All values are calculated after excluding intra-specific interactions.
215
216

217 *Application of the SSM to gut microbiome data*

218 We applied the SSM to the time-series data of gut-microbiota taken from the faeces of six male
219 C57BL/6J mice (M_1 to M_6) which were maintained in a vinyl isolator over a 72 week period
220 (Nakanishi et al. in prep., see Materials and Methods). Because only 18 data points were obtained

221 per mouse (sampled once every 4 weeks between 4 to 72 weeks of age), we performed network
222 inference by aggregating the data of five mice and selected the network that best explained the
223 dynamics of the remaining sixth mouse. We regard that network as the most relevant network. The
224 most relevant networks are inferred using the 4-40 week and 36-72 week data points, considering
225 the shift in community composition around the middle of mouse's aging processes (Nakanishi et al.
226 in prep.). For the 4-40 week time-series data, the most relevant networks had small number of links
227 (18 in total), and it was difficult to determine any characteristic patterns shared among mice (Fig.
228 S3). In contrast, for the 36-72 week time-series, the most relevant networks had many links (52 in
229 total), where 2.6 individuals on average shared any one link (Fig. 4). This was greater than the
230 bootstrap 95% confidence level (2.5) calculated from the surrogate data. All links found within more
231 than four mice (except for those included as "others") included an unclassified Clostridiales, that
232 exhibited a positive relationship between *Allobaculum* and the Clostridiales, the positive effect from
233 the Clostridiales to an unclassified S24-7 (*Bacteroides*) and a *Lactobacillus* to the Clostridiales and
234 the negative effect from an unclassified Rikenellaceae to the Clostridiales.
235



236

237 Figure 4. Interaction networks of six mice inferred by data points at 36-72 weeks of age. (a) to (f)
238 corresponds to mouse M₁ to M₆. Positive and negative effects are indicated by blue and red arrows
239 respectively. The size of the nodes indicates the relative abundance. The thick arrows indicate the
240 links whose strength is in the top 40% among all the links. Inter-specific links are not shown.

241

242

243 **Discussion**

244 We developed the sparse S-map method (SSM), an equation-free method used for inferring
245 ecological interaction networks from a multivariate ecological time-series (Fig.1). Using simulated
246 multispecies population dynamics, we compared the performance of the SSM to a comparable
247 equation-based method, sparse linear regression (SLR), to highlight the differences between
248 equation-free and equation-based methods when applied to complex microbial dynamics. The SSM
249 outperformed SLR in both accuracy and precision, and showed particularly remarkable precision
250 when weak (less than three) links are filtered out (Fig. 2). Furthermore, both mean accuracy and
251 precision of the SSM outperformed that of SLR for all the dataset sizes and observational errors we
252 tested (Fig. 3), with 90% mean precision when the weak links are filtered out (Fig S2). As an
253 equation-free method, the SSM has greater ability to determine species interactions in complex
254 ecological dynamics than the comparative equation-based method, and the performance is robust
255 against observational errors. It is worth noting that increases in the dataset size raised the
256 sensitivity of both methods (Fig 3.b,f,j) and the number of networks that contain strong links (Fig.
257 2S), but might not affect accuracy and precision in general.

258

259 We then applied the SSM to the time-series of gut-microbiota taken from the faeces of six mice.
260 Here, the procedure of applying the SSM to mouse gut microbiota can be regarded as a cross-
261 validation test for the universality of the interaction network among mice. Our results suggested
262 that in the middle to old age (36-72 weeks old), the mice had similar interaction networks, which
263 were characterized by the high connectivity of an unclassified Clostridiales. However, in the young
264 to middle age (4-40 weeks old), there was almost no network pattern common among mice. Hence,
265 the result validates universality in the interaction network only in the latter half of the lifelong
266 dynamics of mouse gut microbiota. This might be due to transitivity of microbial interactions during
267 the development of physiological and immunological functions as well as that of the development of
268 the gut microbiota itself. Recently, Odamaki et al. (2016) showed the age related compositional
269 shifts in human gut microbiota. We anticipate that applying SSM to human subjects in different age
270 groups will offer deeper insights into how the human gut microbiota shaped through its lifelong
271 developmental processes.

272

273 While we adapted a Holling Type III functional response identically to all species relationships in
274 the simulation, a variety of processes will be the source of non-linear species relationships in
275 empirical microbial communities. The complex interdependency of metabolism (Baran et al. 2015),
276 inter specific competition (Hibbing et al. 2010), intercellular signaling such as quorum sensing
277 (Atkinson and Williams 2009), formation of multi-species complexes known as biofilms (Stoodley et
278 al. 2002), and evolutionary processes running concurrently to ecological processes (Gomez et al.
279 2016) might all contribute to the mechanistic basis. The relative performance of the SSM to SLR

280 will depend on the ubiquity and strength of these processes. In this case, large non-linearity indices
281 characterized the dynamics of mouse gut-microbiota (Fig. S4), indicating the effects of nonlinear
282 relationships. Together with the performance of the SSM shown here, the need of equation-free
283 approaches for the analysis of microbial dynamics is demonstrated.

284

285 In the near future, advances in metagenomic technology will further reduce the cost to collect time-
286 series data and its output will be much more accurate and precise. One important question to ask is
287 whether this will allow the replacement of equation-free approaches with equation-based
288 approaches that utilize advanced modelling techniques (e.g., Brunton et al. 2016). There are two
289 reasons why this seems improbable. First, the complex nature of microbial interactions we have
290 described, even with such data, still present difficult challenges in formulating all the present
291 relationships into mathematical formulations (De Angelis 2015, Perretti et al. 2013a, Perretti et al.
292 2013b, Hartig and Dormann 2013). Second, a theoretical study proved that finding a precise
293 dynamical equation for a time-series is, in general, computationally intractable even with any
294 amount/quality of data (Cubitt et al. 2012). Conversely, these data advances would simply benefit
295 our approach by promoting its ability to find links between species. In addition, Ye and Sugihara
296 (2016) suggested a way to utilize high dimensionality of data to harness the predictive ability of
297 equation-free forecasting. Thus, the future development of metagenome technologies would
298 reinforce both the applicability and reliability of equation-free approaches and help improve our
299 mechanistic understanding of microbial communities. We agree with DeAngelis et al. (2015), who
300 stressed the value of equation-free approaches for the analysis of complex dynamical systems.

301

302

303 **Materials and Methods**

304 *Data processing*

305 We assume that time-series $X = \{x(t)\}_{t=1}^L$ is an array of vectors $x(t) = \{x_i(t)\}_{i=1}^N$ where $t = 1, \dots, L$
306 indicates data points with a constant interval (say 1 day), $i = 1, \dots, N$ indicates species (OTUs) and
307 $x_i(t)$ is the abundance of species. If $x_i(t)$ is the relative abundance, then $\sum_i x_i(t) = 1$. However, we do
308 not specify whether x_{it} is relative abundance or absolute abundance because our method is
309 applicable to both cases. For convenience, we assume that $X_i = \{x_i(t)\}_{t=1}^L$ is the time series of species
310 i . We also define a time series $Y = \{y_i(t)\}_{t=1}^{L-1}$, with $y_i(t) = \log x_i(t+1) - \log x_i(t)$, to apply gradient
311 matching (Elnor et al. 2002), which assumes $y_i(t)$ as the response variable and x_t as the
312 explanatory variable. In the regression processes, the explanatory variables and the response
313 variable having the same time index is treated as a pair $(x(t), y_i(t))$. We refer to the set of these
314 pairs $D = \{(x(t), y_i(t))\}_{t=1}^{L-1}$ as “data”.

315

316 *Bootstrap aggregation*

317 Because forward stepwise regression as explained below is known to be unstable, we used a
318 bootstrap aggregation (“bagging”) method to obtain a stable result. To apply the bagging procedure,

319 half of the pairs in D are randomly sampled to make a “database” D_{db} and rest of the points are
 320 assumed as a “target” D_{tg} . We use $\bar{Y} = \{\bar{y}_i(t)\}$, $\bar{X} = \{\bar{x}(t)\}$ and $\bar{x}(t) = \{\bar{x}_i(t)\}$ when we need to
 321 specifically indicate the points in D_{tg} . The process of forward stepwise regression is repeated γ_M
 322 times with different partitioning. Here, we set $\gamma_M = 100$.

323

324 *S-map*

325 S-maps is a locally weighted multivariate linear regression scheme that approximates the best local
 326 linear model by giving greater weight to points on the attractor that are close to the current
 327 ecosystem state. This approach does not require presupposed mathematical formalization of the
 328 target dynamics, and thus regarded as an equation-free modeling approach (empirical dynamic
 329 modelling; Deyle et al. 2015, Ye et al. 2015, Deyle et al. 2013, Sugihara et al. 2012).

330

331 Algorithm 1: S-map

332 1. Initiate $\theta = 0$.

333 2. Select a pair $(x(s), y_i(s))$ from D_{tg} .

334 3. Calculate weight vector by,

$$335 \quad w_s = \left\{ \exp \left(- \frac{\theta \|\bar{x}(s), x(k)\|}{d_s} \right) \right\}_{x(k) \in D_{db}},$$

336 where,

$$337 \quad d_s = \frac{1}{n} \sum_{x(k) \in D_{db}} \|\bar{x}_s, x_k\|.$$

338 Here, $\|\cdot, \cdot\|$ denotes the Euclidian distance between two vectors and $n = |D_{db}|$ is the number of
 339 elements in D_{db} .

340 4. Generate a weighted design matrix as,

$$341 \quad A_s = \{w_{sk} x_k\}_{k=1}^n,$$

342 where w_{sk} is the k th element of w_s .

343 Similarly, generate a vector of weighted response variable as,

$$344 \quad B_s = \{w_{sk} y_i(k)\}_{k=1}^n.$$

345 5. Solve a linear equation

$$346 \quad B_s = A_s C_s,$$

347 as,

$$348 \quad C_s = A_s^{-1} B_s.$$

349 Here, A_s^{-1} is the pseudoinverse of A_s .

350 6. Prediction for $\bar{y}_i(s)$ is obtained as,

$$351 \quad y_i^*(s) = C_s x(s).$$

352 7. Iterate 2-6 until all pairs in D_{tg} is selected. Then, calculate

$$353 \quad MSE_{new} = \frac{\sum_{\bar{y}_i(s) \in D_{tg}} (y_i^*(s) - \bar{y}_i(s))^2}{|D_{tg}|}.$$

354 8. If $\theta = 0$, or $\theta \neq 0$ and $MSE_{new} < MSE$ increment θ by $d\theta$, set $MSE = MSE_{new}$ and back to 2, else

355 return MSE .

356

357 The i th column of the inferred interaction matrix, $c_i^* = \{c_{ij}^*\}_{j=1}^N$ is obtained by simply assuming that

$$358 \quad \tilde{c} = \frac{1}{n} \sum_{k=1}^n C_k,$$

359 and set $c_{ij}^* = \tilde{c}(j)$ for $j \in I_{\text{active}}$ and $c_{ij}^* = 0$ otherwise. Here, $\tilde{c}(j)$ represents the element of \tilde{c}
360 corresponding to the j th species in I_{active} . As explained in the next section, I_{active} is the set of the
361 index of species whose interaction to species i is active (thus, non-zero).

362

363 The parameter θ tunes how strongly the regression is localized to the region of state space around
364 each \bar{x}_s . It is also used as an indicator for the degree of non-linearity of dynamics (Sugihara 1994).
365 Note that if $\theta = 0$, the S-map model reduces to a vector auto-regression (VAR) model. Thus, S-maps
366 include linear VAR models as a special case. More importantly, this also means that the SSM
367 includes SLR as a special case. For $\theta > 0$, the elements of w_s can vary with the location in the state
368 space in which (x, y_i) is plotted, and with increasing θ they can vary more strongly for different \bar{x} .
369 If θ is too small, the coefficients will underestimate the true variability in interaction strength.
370 However, with larger θ the regression hinges on only the most proximal points on the manifold and
371 will therefore be more sensitive to observation error. Here, we selected θ that minimizes MSE by
372 incrementing θ from zero by $d\theta = 0.2$ steps because as a function of θ , MSE generally has a global
373 minima not very distant from zero (say, $\theta < 10$). It is the simplest procedure for the minimization of
374 MSE adopted for explanation, and would be replaced by a more sophisticated method.

375

376 *Forward stepwise regression*

377 The use of forward stepwise regression is motivated by two reasons (Fisher and Mehta 2014). The
378 first reason is that the forward stepwise selection can distinguish between the presence and absence
379 of species interactions and include interactions only when it improves the predictive power of model.
380 This makes inferred interaction networks sparse and easily interpretable. The second reason is that
381 modern metagenomic techniques can only measure the relative abundances of microbes, not their
382 absolute abundances. Hence, the design matrix for the linear regression becomes singular, and
383 there exists no unique solution to the ordinary least squares problem. In the forward stepwise
384 procedure interactions and species are added sequentially to the regression as long as they improve
385 the predictive power of the model. Because the design matrix now only contains a sub-set of all
386 possible species, it is never singular and the linear regression problem is well-defined. Below, we
387 describe the forward stepwise regression including bootstrap aggregation. Since all of the
388 regressions are performed independently for each species, we described the algorithm for a species,
389 i.e. inferring a row of the interaction matrix (c_i^*). The full interaction matrix is obtained by repeating
390 the procedure from $i = 1$ to N .

391

392 Algorithm 2: Forward stepwise regression with bootstrap aggregation

393 1. Set the target species i .

394 2. Initiate index $\gamma = 1$.

395 3. Sample half of the pairs in D to make D_{db} , and set the rest as D_{tg} .

396 4. The set of the index of explanatory variables (species) that have active interactions to species i is
 397 initialized to $I_{active} = \{i\}$ because the presence of intra-specific interaction is natural, and the
 398 interaction with the rest of the species is unified as $I_{inactive} = \{j\}_{j \neq i}$.

399 5. A regression for y_i by $\{x_k\}_{k \in I_{active}}$ is performed by S-map. This returns MSE_{prev} .

400 6. For each index j in $I_{inactive}$, create $I_{test}^{(h)} = I_{active} \cup \{j\}$, where the suffix h indicates that j is the
 401 h th element of $I_{inactive}$.

402 7. Perform a regression y_i by $\{x_l\}_{l \in I_{test}^{(h)}}$ by S-map.

403 8. Repeat 7 to obtain $MSE^{(h)}$ for all h .

404 8. Set the least $MSE^{(h)}$ as MSE_{best} and $I_{test}^{(h)}$ as I_{best} .

405 9. If $Q = 1 - MSE_{prev}/MSE_{best}$ is greater than a pre-specified value (Q_c) then set MSE_{best} as

406 MSE_{prev} and I_{best} as I_{active} , remove h th element of $I_{inactive}$ and go back to 6, otherwise go to 10.

407 10. Return $c_i^*(\gamma)$ where γ indicates that the inferred interaction strength for species i is obtained
 408 by the γ th iteration. If $\gamma < \gamma_M$ increment γ_M by 1 and go back to 3, otherwise terminate the loop.

409 10. Return $c_i^* = \text{Median}(\{c_i^*(\gamma)\}_{\gamma=1}^{\gamma_M})$.

410

411 Q_c controls the sensitivity of the algorithm to find links between species. It is reasonable to fix Q_c
 412 to zero because this means that a new link will be accepted as long as it improves MSE . Thus we
 413 set Q_c to zero in both the SSM and SLR unless otherwise mentioned.

414

415 *Simulation model*

416 We used a population dynamics model to generate the data set for validation. The model is based on
 417 a generalized Lotka-Volterra equation (GLVE),

$$418 \quad \frac{dx}{dt} = x_i \{G(x_i) + \sum_{j=1}^N F_i(x_j)\},$$

419 (1)

420 which has been frequently used to model microbial population dynamics (Bucci et al. 2016, Coyte et
 421 al. 2015, Fisher and Mehta 2014). Here, $G(x_i) = r_i(1 - \sum_{i=1}^N x_i/K)$ and $F_i(x_j) = c_{ij}x_j^2/(\beta + x_j^2)$. F_i is
 422 known as the Holling Type III functional response and introduces nonlinear species relationships. r_i
 423 is the intrinsic growth rate and K is the carrying capacity that defines upper limit of abundance.
 424 Here, the metagenomic read count roughly corresponds to K . c_{ij} represents the effect of species j
 425 on i . Thus, the matrix $C = \{c_{ij}\}$ expresses the “true” interaction between species except for where
 426 $i = j$, in which the effect of the first and second terms in (1) cannot be divided. β is the half-
 427 saturation constant of the interspecific interaction and controls the strength of non-linearity within
 428 the population dynamics.

429

430 To reduce the right hand side of equation (x), we used the relationship,

431
$$\frac{1}{x} \frac{dx}{dt} = \frac{d \log x}{dt}.$$

432 Hence eq. (1) is transformed to,

433
$$\frac{d \log x}{dt} = G(x_i) + \sum_{j=1}^N F_j(x_j).$$

434 (2)

435 The discrete nature of metagenomics data is captured by discretizing eq. (2) as,

436
$$\log x_i(t + \Delta t) - \log x_i(t) = \{G(x_i) + \sum_{j=1}^N F_j(x_j)\} \Delta t.$$

437 By setting $\Delta t = 1$ without loss of generality and introducing demographic stochasticity, we obtain
438 the equation describing the population dynamics as,

439
$$\log x_i(t + 1) = \log x_i(t) + G(x_i) + \sum_{j=1}^N F_j(x_j) + \eta_i(t) / \sqrt{x_i(t)}.$$

440 (3)

441 Here $\eta_i(t)$ is a random value drawn from a normal distribution with mean 0 and variance σ^2 . σ^2
442 determines the strength of stochasticity relative to the deterministic processes.

443

444 One can easily see that eq. (3) is transformed to,

445
$$y_i(t) = \log x_i(t + 1) - \log x_i(t) = G(x_i) + \sum_{j=1}^N F_j(x_j) + \eta_i(t) / \sqrt{x_i(t)}.$$

446 (4)

447 This equation gives the true relationship between x 's and y_i when applying the regression test. It
448 is worth noting that, although we specify G and F here, the SSM does not require F and G to be
449 known or even described as a specific mathematical formulation. It should be noted that due to the
450 form of F we adopted, the inferred interaction strength is roughly scaled as $c_{ij}^* \sim c_{ij}/K$. Hence we
451 rescaled it as $c_{ij}^* \rightarrow Kc_{ij}^*$.

452

453 *Data generation*

454 We used eq.(4) to generate ground truth data as follows. We generated the initial state as $\{10^{\xi_i}\}_{i=1}^N$

455 where ξ_i is a random value drawn from a uniform distribution (0,4) and N is the number of
456 species. The interaction matrix C is generated by the following rule; (1) C must have $(N^2 - N)/2$
457 non-zero elements, (2) value of a non-zero element is randomly assigned from a uniform distribution
458 $(-2, -0.05)$ or $(0.05, 2)$ and (3) $c_{ji} \neq 0$ if $c_{ij} \neq 0$. With this initial state and interaction matrix, we
459 numerically solved eq.(4) up to 5000 steps and took the latter 200, 100 or 50 steps. The numerical
460 simulation was discarded if the abundance of at least one species fell below one; otherwise the result
461 was sampled every 2 steps to make a time-series with 100, 50 or 25 data points.

462

463 Other parameter values were as follows. We set $r = 1$ so that the scale of dynamics was relevant to
464 the simulation of microbial dynamics observed as the time-series of 100, 50 and 25 data points.

465 Intra-specific competition ($c_{ii} < 0$) was -0.4 . This controlled the balance between stability and

466 instability. For example, a species does not coexist if c_{ii} is too large, while most communities
467 converge to an equilibrium if c_{ii} is too small. The variance coefficient of process noise was set to
468 $\sigma^2 = 0.04$. This became a source of complexity within time-series data at a certain level. K was set
469 to 10^4 considering the standard size of a metagenomic read count. Finally, we set β to $0.05 \times K^2$ to
470 introduce non-linear effects throughout the functional response. Because these values are for the
471 specific Lotka-Volterra equation we used, except for two parameters (r and K) specified by general
472 criteria, discussion of whether the parameter values are valid for microbial systems or not is not
473 important. Instead, the parameter values were adjusted so that the GLV model constantly
474 generated dynamics that satisfied the acceptance criteria $\theta > 1$, because the relative performance of
475 the SSM is in general higher than SLR if θ deviates from zero. The Holling Type III functional
476 response was also adapted because it reduces extinctions and non-persistent chaos in multispecies
477 communities (Williams and Martinez 2004).

478

479 *Nonlinearity of time-series*

480 We evaluated the non-linearity of time-series by calculating θ_i as follows.

481

482 Algorithm 3: Calculation of θ_i

- 483 1. Set the target species i .
- 484 2. Initiate index γ to 1.
- 485 3. Sample half of the pairs in D to make D_{db} , and set the rest to D_{tg} .
- 486 4. A regression for y_i by x is performed by S-map and set θ that minimizes MSE as $\theta_i^{(\gamma)}$ and
487 increment γ by 1.
- 488 5. Back to 3 if $\gamma < \gamma_m$, otherwise terminate the loop.
- 489 6. Set the mean of $\theta_i^{(\gamma)}$'s to θ_i .

490

491 Here, we set γ_m to 24. We accepted the time-series only if $\text{Min}(\{\theta_i\}_{i=1}^N) > 1$ is satisfied.

492

493 *Observational error*

494 To simulate observational error, each abundance data $x_i(t)$ was perturbed by a random value
495 drawn from a normal distribution with mean zero and variance $\varsigma x_i(t)$. Here, we used six different
496 values (0,1,2,4,8,16) for ς .

497

498 *Application of the SSM to mouse microbiome data*

499 In the mouse gut microbiome data we used, OTUs were categorized into genus-level groups by the
500 CLASSIFIER program of the Ribosomal Database Project (RDP) within a software package
501 Quantitative Insights into Microbial Ecology (QIIME). For detailed description of this data set see
502 Nakanishi et al. (in prep.). For our analysis, we picked the seven most abundant groups that
503 comprise approximately 85% of the total microbial biomass and classified the abundance of the
504 remaining groups into a single group of "others". Next, (x, y_i) was calculated for all mice and one

505 mouse (M_k) selected as the test dataset. The remaining mice ($\{M_l\}_{l \neq k}$) were used as the training
506 data for cross validation which was aggregated to form dataset D . The SSM was performed on D as
507 described above but instead of accepting the last step before Q_c exceeded zero, I_{active} of each step in
508 a forward stepwise regression was stored for $0.2 < Q_c < -0.2$. Then, the value of I_{active} that
509 minimizes the MSE of S-map predicting y_i from x in the test data was selected and c_i^* was
510 calculated as per the explanation of S-map. The above procedure was repeated for all groups in k to
511 form the M_k 's most relevant network. θ_i 's values were also calculated for M_k using Algorithm 3
512 (Fig. 4S).

513

514 *Data accessibility*

515 The mouse gut microbiome data is available in the DDBJ database (<http://getentry.ddbj.nig.ac.jp/>)
516 under accession number DRA004786. We used Mathematica 10.2 to implement the SSM and SLR,
517 generate simulation data, process mouse gut microbiome data and to perform analysis. Computer
518 codes (Mathematica notebook files) can be provided upon request to the authors.

519

520

521

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649

650

651 **Author contributions**

652 K.S. conceived and designed the project, developed the SSM, performed numerical simulations and
653 analyzed all the real data. All authors analyzed the results, wrote the manuscript and approved the
654 final version of the manuscript.

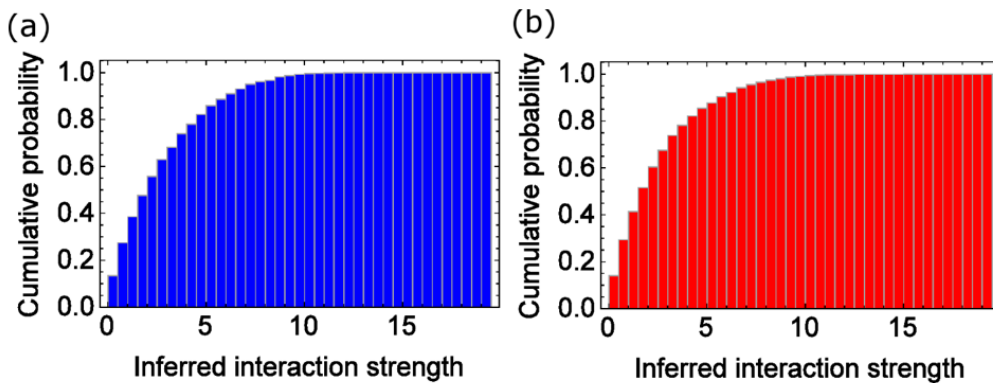
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658 **Supplementary figures**

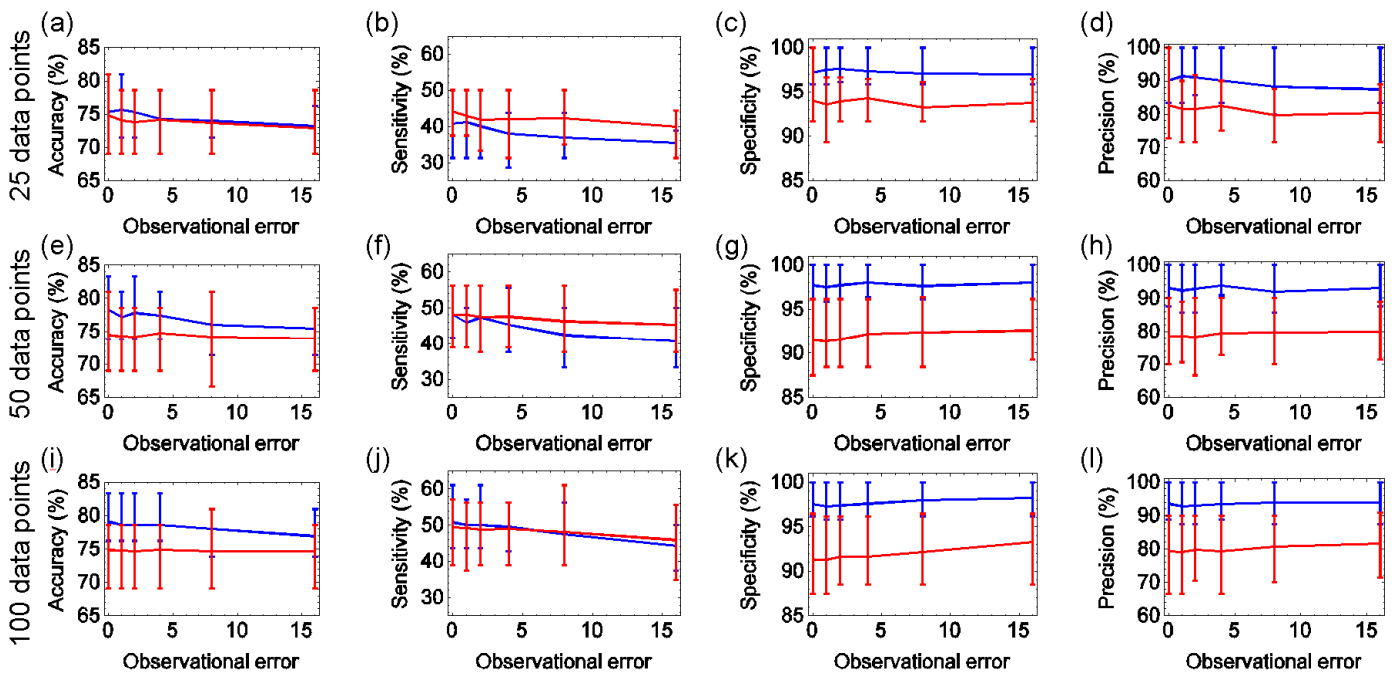
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661 Figure S1. Cumulative distribution of inferred interaction strength in figure 2a for SSM (a) and
662 SLR (b).

663

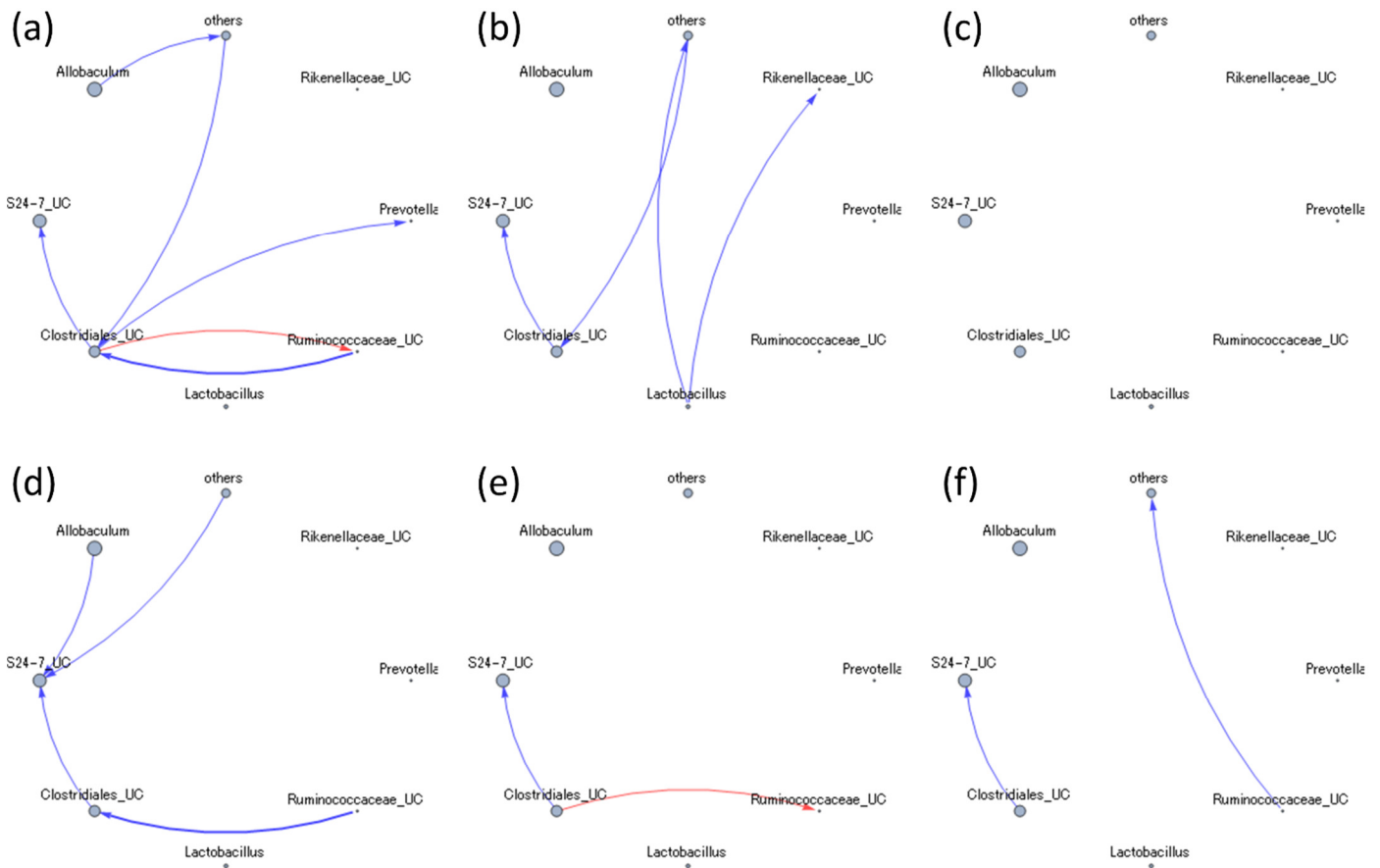


664

665 Figure S2. Robustness of SSM and SLR for observational errors and data size for networks where
666 weak (fewer than three) inferred interactions are filtered out from the results of figure 3. Accuracy,
667 sensitivity, specificity and precision for different observational errors were calculated for time-series
668 with 25 data points (a-d), 50 data points (e-h) and 100 data points (i-l) sampled from simulated
669 ecological dynamics. Blue lines indicates SSM and red lines indicate SLR. Solid lines indicate the
670 mean value and the error bars indicate the first and the third quartiles. Among 100 trials, about
671 20% of the networks inferred by 50 data points and 40% of that of 25 data points were not included
672 because they had no inter-specific links.

673

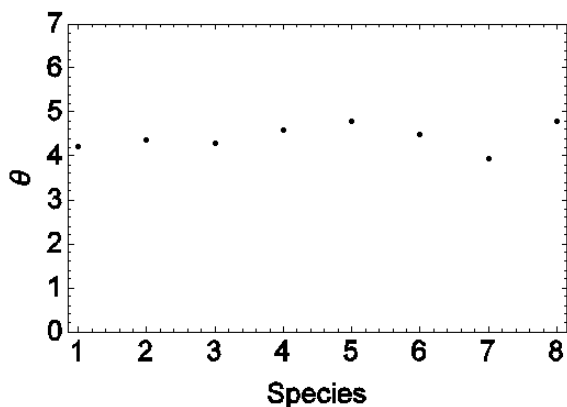
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675

676 Fig. S3. Interaction networks of six mice inferred by 4-40 weeks old (a-f). Positive and negative
 677 effects are indicated by blue and red arrows respectively. The size of nodes indicates relative
 678 abundance. Inter-specific links are excluded.

679



680

681 Fig. S4. θ_i of M_1 calculated for all (18) data points. Indices 1-8 corresponds to, *Allobaculum*, *S24-7*,
 682 *Clostridiales*, *Lactobacillus*, *Ruminococcaceae*, *Prevotella*, and *others*, respectively. θ_i s are not
 683 significantly different for other mice.