1   **Title**: A new conceptual framework for host-microbe symbiosis

2   **Keywords:** symbiosis; transmission mode; partner fidelity; fitness effects

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9   **Abstract**:

10   Host-microbe relationships are studied across biological disciplines, with different but related

11   discipline-specific conceptual frameworks arising from each of them. Without a unified framework

12   that can be applied across all symbioses, we cannot do the interdisciplinary work necessary to

13   understand the underlying rules that govern symbiosis. Here I present a new conceptual framework

14   for host-microbe symbiosis, rooted in its original definition, across three axes of fitness effects,

15   partner fidelity and transmission mode. The three axes make a cube where any symbiotic

16   relationship can be placed. The position of a particular symbiosis is fluid and context-dependent,

17   changing through evolution and throughout the lifetime of an organism. The three axes make for a

18   simple and inclusive framework for symbiosis. We can use this framework to examine every known

19   symbiosis, we will be able to understand the rules and patterns that govern them.

20

Introduction:

Symbiosis is a commonly used and contentiously argued term. It was first coined by De Bary in 1879, often quoted as "the living together of unlike organisms" but in the English translation by Oulhen et al. [1] "the living together of differently named organisms". Regardless of the exact wording, one important point is that, within this definition, symbiosis ranges from mutualistic interactions where both partners benefit, to parasitic ones, where one partner benefits while the other is harmed. It has long been accepted that these relationships exist on a spectrum rather than in discrete categories [2–4]. This shift in thinking has allowed us to see that there are commonalities and contrasts in how parasites, commensals and mutualists interact with their symbiotic partners [5]. It also allows us to think about how these relationships change: besides a few notable symbioses that abruptly transition between categories, generally, symbioses shift along the fitness continuum with a changing ecological context.

There is some debate around the bounds of symbiosis, particularly as it relates to the level of intimacy between symbiotic partners. While I am of the opinion that we can expand this framework to include all relationships that one would consider mutualist, commensal and parasitic, for the purposes of this perspective, I focus only on symbioses involving at least one microbial partner. While it is commonly accepted that symbiotic relationship exist along a spectrum of fitness effects, in this new framework I introduce two additional axes, allowing us to compare different symbiotic relationships in multidimensional space. My hope is that this conceptual framework can be used across disciplines to provide a unified definition and framework for host-microbe symbiosis. By having a unified conceptual framework, I believe that we will be better equipped to understand patterns in how symbioses occur and change in nature.

Fitness effects

45

46   As I briefly introduced above, the first axis of symbiosis to consider is that of fitness effects,

47   namely, how two organisms in a symbiotic relationship affect each other's fitness (Figure 1A). A

48   mutualistic relationship is one where both partners benefit. Some classic examples of mutualism

49   include aphids and *Buchnera* bacteria [6], bobtail squid and *Vibrio fischeri* [7], humans and *Bifidobacteria*

50   [8], algae and fungi in lichens [9] and legumes and nitrogen-fixing rhizobia [10].

51   Parasitism exists at the opposite end of the spectrum of fitness effects, where one partner

52   benefits at a fitness cost to the other partner. These relationships include those that are traditionally

53   grouped under the category of medical parasitology such as tape worms, lice, and *Giardia* [11], but

54   also any organism that is considered a pathogen, such as HIV [12] and pathogenic *Salmonella* in

55   humans [13] chytrid fungi that causes chytridiomycosis in amphibians [14], and *Escovopsis* in the

56   fungus gardens of leaf-cutter ants [15].

57   Between mutualism and parasitism lies commensalism, where one partner benefits and the

58   other experiences no fitness effects. Many examples of phoresy, where a smaller organism uses a

59   larger organism for dispersal, are considered commensal [16]. It is important to note that in the

60   human microbiome literature, symbionts that benefit their host are often incorrectly called

61   commensals, rather than mutualists [17]. This is the unfortunate result of the history of human

62   microbiology having been rooted in studying pathogens. Because of this, anything that did not cause

63   disease to the human host was lumped into the category of commensal, even if it benefitted the

64   host. My hope is that we can change this terminology to bring it in line with the ecological origins of

65   the term, but until then, it is important that we always define our terms when presenting our

66   microbiome and symbiosis studies.

67   Every symbiotic relationship lies somewhere on the axis of fitness effects. However, its

68   position along the axis is not static, and can change through evolution and across ecological time

69 and space. There are countless examples of instances of change across the fitness effects axis:

70 commensal microbes becoming opportunistic pathogens when the host's immune system is

71 compromised [18], the breakdown of the mutualism between corals and Symbiodiniaceae during

72 coral bleaching [19] and mutualistic endophytes evolving from latent pathogens [20]. Some

73 relationships are less context-dependent than others. For example, the relationship between fungus-

74 growing ants and their cultivar is always a mutualism. This relationship has co-evolved for tens of

75 millions of years, and there is very little that can move the relationship from this position [21]. But

76 even within the mutualism space, one ant colony may serve as a more effective disperser and so

77 would provide greater fitness benefits to the fungus compared to a colony with less effective

78 dispersal. In this case, the relationship would not switch from being a mutualism to a parasitism, but

79 if we compared the two ant colonies across the axis, one would be further toward the extreme end

80 of mutualism than the other. This variation in symbiosis-related fitness effects between members of

81 a population, along with the variation in the environment in which the relationships exist, are the

82 fodder for evolutionary change across the axis.

83 **Partner fidelity**

84   Symbioses are often categorized as falling into one of two discrete levels of partner fidelity:

85 obligate or facultative. Classically, obligate is the case when at least one partner cannot survive

86 without the other, and facultative is when there may be fitness effects in a symbiosis, but the

87 partners can still survive without the other. I argue that the concept of a facultative symbiosis is just

88 a way to capture the inherent context-dependency of partner fidelity. We see this in the relationship

89 between legumes and their root symbiont rhizobia bacteria. This symbiosis is used as a classic

90 example of a facultative mutualism. If a legume plant is grown in nitrogen-rich soil, the number of

91 root nodules that it produces are reduced because this function is not necessary for the plant [22].

92 One could argue that *when nitrogen is present* in the soil, this relationship is facultative. However, what

93   happens if you grow this plant in soil with no nitrogen at all? I argue that this plant can no longer

94   survive without its mutualistic partner, and so the relationship would become obligate. In this case,

95   the partner fidelity depends largely on the availability of nitrogen in the local environment.

96   As the legume/rhizobia example illustrates, instead of defining obligate and facultative as

97   discrete categories as we have always done, I think we should describe fitness effects along a

98   context-dependent axis (Figure 1B). At one end we have obligate relationships where the partner

99   pair is always together, at the other end we have no fidelity where the pair is never together, and

100 everything in the middle is facultative. As a relationship reaches no fidelity it will cease to be a

101 symbiosis. Where a relationship lies on the spectrum from obligate to no fidelity will depend on

102 context, and the position can change across ecological and evolutionary time scales. Like the fitness

103 effects axis, the flexibility of the position along the partner fidelity axis will vary for symbiotic

104 partners. There are some relationships in nature that we could classify as strictly obligate. *Chlamydia*

105 and many other intracellular parasites can only reproduce inside of host cells, and so context matters

106 less for the position of the relationship between *Chlamydia* and its host along this axis [23] .

107   Finally, the position along this axis will depend on which partner we are considering in the

108 relationship. In the case of *Chlamydia* (and other parasites) the relationship for the symbiont can be

109 obligate, but clearly, the host can and does survive without the symbiont. Therefore, the relationship

110 is obligate for the parasite but there is no fidelity from the perspective of the host, making this a

111 one-sided symbiotic relationship. Even for mutualisms, we can have one-sided symbioses. Corals

112 have an obligate relationship with Symbiodiniaceae but the algae can be free-living in the water

113 column. These asymmetrical relationships will be discussed further in the "three axes make a cube"

114 section.

115

116 **Transmission mode**

117   Transmission mode of a symbiont can vary widely, having important effects on the nature of

118   the relationship, and exists across a continuum that can vary depending on context (Figure 1C). At

119   one end of the spectrum is vertical transmission, which is from a parent to offspring. At the other

120   end of the spectrum is environmental transmission, which is when a symbiont is acquired from the

121   environment. Horizontal transmission is that which occurs between two conspecifics, and in this

122   axis, exists in the middle. Transition mode is one measure of intimacy of a relationship [24]. Vertical

123   transmission is the most intimate, and environmental acquisition is the least, but there is variation

124   within each of these classic categories, and our understanding of symbioses would be improved if we

125   put them along a spectrum, rather than discrete categories.

126   A classic example of strict vertical transmission is that of aphids and *Buchnera* bacteria, which

127   the aphids house in specialized organs called bacteriocytes. The parent aphid uses a precise

128   mechanism for ensuring the *Buchnera* is transmitted from its bacteriocyte into the embryo [25].

129   Vertical transmission can happen in a slightly less intimate way as well. For example, when a human

130   gives birth through the vaginal canal, the infant receives its initial microbiome from the parent. But

131   the infant also receives some members of its microbiome during the process of breastfeeding and by

132   sharing intimate space with its birthing parent [26]. At what point do we consider transmission of

133   symbionts from parent to offspring vertical transmission vs horizontal transmission from individuals

134   who happen to be the child's parents? Notably, if a child acquires symbionts from breastfeeding

135   from a non-parent individual, then this would be considered horizontal transmission even though

136   the process of acquisition is the same. Depending on the nature of the relationship between

137   symbiotic partners, particularly whether they are endosymbionts, categorization between horizontal

138   and vertical transmission exists on a continuum and is context-dependent.

139   This can also be said when considering the difference between environmental transmission

140   and horizontal transmission. Let's consider the example of SARS-CoV-2. If someone infected with

141   the virus infects another person through close contact, this would be horizontal transmission.

142   However, if someone coughs the virus out in a room and it remains suspended in the air for several

143   hours then another person walks in and breathes it in, the transmission mode would exist

144   somewhere between horizontal and environmental transmission [27]. There are other symbionts, for

145   example HIV or *Chlamydia*, that cannot be environmentally transmitted – they must be either

146   horizontally or vertically transmitted because they cannot persist outside of a host's tissues. Once

147   again, the position of a relationship along this axis is context-dependent but the level of context-

148   dependency varies from one relationship to another.

149   While on the topic of transmission mode, let's discuss the different use of the terms in the

150   marine symbiosis/microbiome world compared to terrestrial. In marine systems, scientists typically

151   use the term horizontal transmission to mean what I define here as environmental transmission. I

152   urge my marine counterparts to consider using the terms as they are defined here since there is a

153   difference in how a symbiont must be adapted, or not, to existing in the environment if it is

154   environmentally transmitted. This is perhaps less relevant for marine systems since moving from the

155   body of an organism through salt water may be a less abrupt of a transition than moving through air,

156   but rather than conflating environmental and horizontal transmission, we can acknowledge that in

157   marine systems, the boundaries between the two can be less rigid. This case further supports using a

158   continuum to explain transmission mode, extending between vertical and environmental

159   transmission, where the position of a particular symbiotic relationship along the axis is context

160   dependent.

161   Importantly, some symbionts are transmitted by vectors or intermediate hosts. This may

162   seem to break the transmission mode axis. Instead, for the purposes of this conceptual framework, I

163   lump vector transmission with environmental transmission. Clearly, these phenomena are very

164   different, but if we focus on just the relationship between the two focal partners in a symbiosis, we

165 can use a separate cube for the relationship between the symbiont and vector. For our focal species,

166 whether a symbiont is transmitted through the environment or through a vector, it still requires

167 some kind of adaptation that allows for it to be separate from its symbiotic counterpart, either to

168 tolerate being in the environment, or to be successfully picked up by a vector. For the sake of

169 simplicity, they can be grouped together on the far end of the transmission mode spectrum from

170 vertical transmission where the symbiont must remain in constant contact with the host.

171 **Three axes make a cube**

172   The only logical thing for me to do when presented with three axes, is to put them together

173 into a cube (Figure 1D). Every symbiotic relationship can be placed somewhere in the three-

174 dimensional space of the cube, occupying a cloud of probability space. In cases where there is not a

175 lot of context-dependent flexibility, the cloud will be small, and where a relationship is heavily

176 context dependent, it will be large. The cloud of possible relationship space will not necessarily be

177 spherical. A relationship may be heavily context-dependent along one axis but not the others.

178 Through either ecological or evolutionary time, many symbiotic relationships may transition

179 gradually across the axis of fitness effects, from commensal to mutualistic or commensal to parasitic,

180 or even from mutualistic through commensal to parasitism. However, this is not the case for all

181 symbiotic relationships. Transitions between mutualism and parasitism can also happen abruptly

182 [28]. In these cases, the cloud of possibilities for a symbiotic pair would not pass through

183 commensalism. Instead, this relationship could be represented by two clouds of possibility at the

184 extremes of the axis of fitness effects. This should be the case for the other axes as well, and indeed
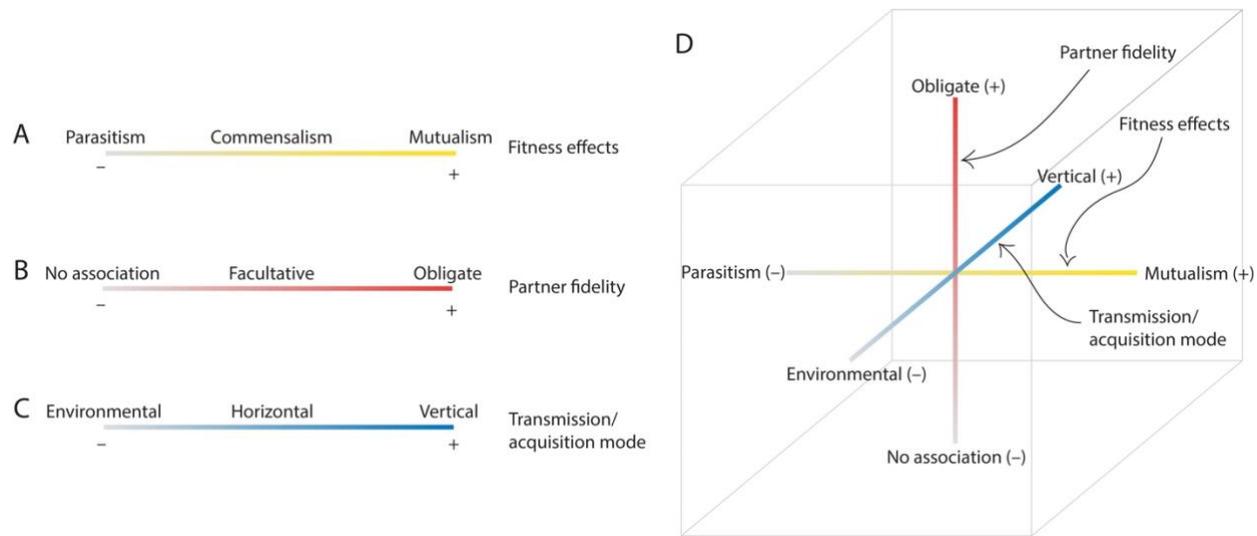
Figure 1 The three axes of symbiosis separately (A, B and C) and as a cube (D).

185   there can also be discrete clouds along the transmission mode axis. For example, dengue virus is

186   typically vector-transmitted but can also be vertically transmitted through umbilical chord blood,

187   however, it is never horizontally transmitted [29].

188   Earlier we encountered the problem of asymmetrical symbioses, particularly for the purpose

189   of partner fidelity (obligate for one partner but not for the other). One solution to this problem is

190   that we emphasize who the focal species is when we create a cube. The natural thing to do is to

191   focus on the host but this only works when there is a clear host. There are plenty of microbe-

192   microbe symbioses, where there is not. Regardless, when we make a cube for a relationship, we

193   should pick a focal species.

194   The cube can be used as a comparative tool to standardize how we describe symbioses. If we

195   populate the cube with every described symbiosis, then we may start to observe interesting patterns

196   or even rules. I expect that we will see more symbioses toward the edges of the cube, largely because

197   as scientists, we are drawn to striking phenotypes. But there may also be patterns that result from

198   the realities of biology. For example, obligate mutualists will tend to be vertically transmitted,

199   whereas parasites will be more likely to be horizontally or environmentally transmitted. One rule that

200 emerges from thinking in this holistic way is that environmentally transmitted obligate symbionts

201 must have a dormant phase. You can see this with viruses – all of them are obligate to their hosts

202 and all of them have a dormant particle phase when they are outside of their host cells. This rule

203 holds for parasites such as *Giardia* and *Chlamydia* as well. Getting to this place, where we can fully

204 populate the cube, will take considerable effort: we will need to agree on ways to standardize and

205 quantify the nature of relationships on the axes, across a wide range of biological systems. I believe

206 that by using this conceptual framework we will have a powerful tool to understand patterns in

207 symbiosis more broadly by examining which parts of the cube are more commonly occupied.

208 Specifically, we can ask questions about the tendencies and the mechanisms behind transitions

209 between locations on the cube. Are there parts of the cube that are harder to occupy and why? Are

210 there certain transitions that are more likely than others? Given a particular ecological context, will

211 the future positioning of a symbiotic relationship be predictable? I believe that by adopting this

212 framework, where each factor of symbiosis is considered along a spectrum, we will more easily be

213 able to answer these types of questions.

214 **Conclusion**

215 　　To end this perspective, I paraphrase Starr (1975) and Lewis (1985) to say that I am neither

216 the first nor will I be the last person to provide a framework to describe and understand symbiosis. I

217 invite you, dear reader, to let me know what you think. Can you imagine using the cube to teach

218 about symbiosis as a concept? Do you fundamentally disagree with me about the bounds of

219 symbiosis? Do you think that we could use this conceptual framework to model and predict the

220 nature of symbiotic relationships? I hope that this perspective can help inspire conversations that

221 can move us closer toward consensus on a universal framework for symbiosis.

222

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