The validity of pairwise models in predicting community dynamics

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Abstract

Pairwise models are commonly used to describe many-species communities. In these models, the fitness of a species is additively affected by its pairwise interactions with every other species ("pairwise additivity assumption"), and all pairwise interactions are represented by a single canonical equation form ("universality assumption"). Here, we analyze the validity of pairwise modeling. We build mechanistic reference models for chemical-mediated interactions in microbial communities, and attempt to derive corresponding pairwise models. Even when one species affects another via a single chemical mediator, different forms of pairwise models are appropriate for consumable versus reusable mediators, with the wrong model producing qualitatively wrong predictions. For multi-mediator interactions, a canonical model becomes even less tenable. These results, combined with potential violation of the pairwise additivity assumption in communities of more than two species, suggest that although pairwise modeling can be useful, we should examine its validity before employing it.

Introduction

Multispecies microbial communities are ubiquitous. Microbial communities are important for industrial applications such as cheese and wine fermentation (van Hijum, Vaughan, and Vogel 2013) and municipal waste treatment (Seghezzo et al. 1998). Microbial communities are also important for human health: they can modulate immune responses and food digestion (Round and Mazmanian 2009; Kau et al. 2011) or cause diseases (Kelly 1980).

Community-level properties (e.g. species composition and biochemical activities) cannot be achieved, or achieved to the same extent, by individual members. Community-level properties are influenced by interactions wherein individuals alter the physiology of other individuals. To understand and predict properties of communities, choosing the appropriate mathematical model to describe species interactions is critical.

Two commonly-used modeling approaches are mechanistic modeling and pairwise modeling, each with its pros and cons. In mechanistic modeling, interaction mechanisms are explicitly modeled (Fig 1A and B, left panels). Thus, a mechanistic model requires discovering and quantifying interaction mechanisms (Fig 1 Table, "parameter" rows under "Mech." column). Such a mechanistic model can in principle quantitatively predict community dynamics when species

evolution is negligible. However, the complexity of microbial interactions and the difficulty in identifying and quantifying interactions have made it challenging to construct mechanistic models.

In contrast to mechanistic modeling, pairwise modeling considers only the fitness effects of pairwise species interactions (Figs 1A and B, right panels). Pairwise models have two central assumptions. First, the "universality" assumption: how one species affects another can be abstracted into a single canonical equation form regardless of interaction mechanisms. Second, the "pairwise additivity" assumption: a focal individual receives additive fitness effects from pairwise interactions with other community members. Even though pairwise models do not capture the dynamics of chemical mediators, predicting species dynamics is still highly desirable in, for example, forecasting species diversity and compositional stability.

Pairwise models are easy to construct because they do not require knowledge of interaction mechanisms and need fewer parameters than mechanistic models (Fig 1 table). Parameters are relatively easy to estimate using community dynamics (Stein et al. 2013), or more systematically, using dynamics of monocultures and pairwise cocultures (Fig 2C).

Not surprisingly, pairwise modeling has been commonly applied to communities (Wootton and Emmerson 2005). Pairwise models are often justified by their success in predicting ecological dynamics of two-species communities of prey-predation (Fig 1-FS1) (Volterra 1926; Wangersky 1978; "BiologyEOC - PopulationChanges" 2016) and competition (Gause 1934a; Gause 1934b). Pairwise modeling has been expanded to model communities of more than two species (defined as *multispecies communities*), with empirical support from, for example, an artificial community of four competing protozoa species (Vandermeer 1969). Multispecies pairwise models have been extensively used to predict how perturbations to steady-state species composition increase or decrease over time (May 1972; Cohen and Newman 1984; Pimm 1982; Thébault and Fontaine 2010; Mougi and Kondoh 2012; Allesina and Tang 2012; Suweis et al. 2013; Coyte, Schluter, and Foster 2015).

However, pairwise modeling has known limitations. For instance, in a multispecies community, an interaction between two species can be altered by a third species (Levine 1976; Tilman 1987; Wootton 2002; Werner and Peacor 2003; Stanton 2003). Indirect interactions via a third species fall under two categories (Wootton 1993). In an "interaction chain" (also known as "density-mediated indirect interactions"), for example a carnivore affects the density of a herbivore which in turn affects the density of plants. In "interaction modification" (also known as "trait-mediated indirect interactions" or "higher order interactions" (Vandermeer 1969; Wootton 1994; Billick and Case 1994; Wootton 2002)), for example a carnivore affects how often a herbivore forages plants. Interaction modification (but not interaction chain) violates the pairwise additivity assumption (Fig 1-Supplementary Text). Interaction modification is thought to be common in ecological communities (Werner and Peacor 2003; Schmitz, Krivan, and Ovadia 2004). Limitation of

pairwise modeling has also been studied experimentally (Dormann and Roxburgh 2005). However, empirically-observed failure of multispecies pairwise models could be due to limitations in data collection and analysis (Case and Bender 1981; Billick and Case 1994).

Given the benefits and limitations and intellectual influences of pairwise modeling, we examine conditions under which pairwise models produce realistic predictions. Instead of investigating natural communities where interaction mechanisms can be difficult to identify, we start with *in silico* communities where species engage in predefined chemical interactions of the types commonly-encountered in microbial communities. Based on these interactions, we construct mechanistic models, and attempt to derive from them pairwise models. A mechanistic reference model offers several advantages: community dynamics is deterministically known; deriving a pairwise model is not limited by inaccuracy of experimental tools; and the flexibility in creating different reference models allows us to explore a variety of conditions. This has allowed us to examine the domain of validity for pairwise modeling.

Results

Establishing a mechanistic reference model

In our mechanistic models (Fig 1A left), we focus on chemical interactions which are widespread in microbial communities (Fig1-FS2) (Stams 1994; Czárán, Hoekstra, and Pagie 2002; Duan et al. 2009). A mechanistic model includes a set of species as well as chemicals that mediate interactions among species. A species $\mathbf{S_i}$ could release or consume a chemical $\mathbf{C_j}$, and chemical $\mathbf{C_j}$ could increase or decrease the growth rate of species $\mathbf{S_k}$.

We assume that fitness effects from different chemical mediators on a focal species are additive. Not making this assumption will likely violate the additivity assumption essential to pairwise modeling. Additive fitness effects have been observed for certain "homologous" metabolites. For example, in multi-substrate carbon-limited chemostats of *E. coli*, the fitness effects from glucose and galactose were additive (Lendenmann and Egli 1998). "Heterologous" metabolites (e.g. carbon and nitrogen sources) likely affect cell fitness in a multiplicative fashion. However, if released mediators cause small changes to the concentrations already in the environment, then additivity approximation may still be acceptable. For example, suppose that the fitness influences of released carbon and nitrogen with respect to those already in the environment are w_c and w_n, respectively. If w_c, w_n<<1, the additional relative fitness influence will be $(1+w_c)(1+w_n)-1 \approx w_c+w_n$. "Sequential" metabolites (e.g. diauxic shift) affect cell fitness in a non-additive fashion. Even among homologous metabolites, fitness effects may be non-additive (Hermsen et al. 2015).

We also assume that resources not involved in interactions are never limiting. We thus simulate continuous community growth similar to that in a turbidostat, diluting the total population to a low

density once it has reached a high-density threshold. Within a dilution cycle, a mechanistic model can be represented by a set of first-order differential equations, as

$$\frac{dS_i}{dt} = \left[r_{i0} + \sum_j r_{S_i C_j} \frac{C_j}{C_j + K_{S_i C_j}} \right] S_i \qquad \text{(Eq 1).}$$

$$\frac{dC_i}{dt} = \sum_j \beta_{C_i S_j} S_j - \sum_j \alpha_{C_i S_j} \frac{C_i}{C_i + K_{C_i S_j}} S_j$$

S_i and C_i are state variables representing the concentrations of species $\mathbf{S_i}$ and chemical $\mathbf{C_i}$, respectively. r_{i0} is the basal fitness of an individual of species $\mathbf{S_i}$ (the net growth rate of a single individual in the absence of any intra-species or inter-species interactions). $r_{S_i C_j}$ reflects the maximal influence of chemical $\mathbf{C_j}$ on the growth rate of $\mathbf{S_i}$, while $K_{S_i C_j}$ is the concentration of $\mathbf{C_j}$ achieving half maximal influence on the growth rate of $\mathbf{S_i}$. $\beta_{C_i S_j}$ and $\alpha_{C_i S_j}$ are respectively the release rate and the maximum consumption rate of $\mathbf{C_i}$ by species $\mathbf{S_j}$. $K_{C_i S_j}$ is the C_i at which half maximal rate of consumption by $\mathbf{S_j}$ is achieved. All parameter definitions are summarized in Fig 1 table.

Deriving a pairwise model

Ideally we would want a canonical pairwise model to represent the fitness effect of one species on another regardless of interaction mechanisms. Specifically, the fitness of a focal species $\mathbf{S_i}$ is the sum of its basal fitness r_{i0} and the additive fitness effects exerted by pairwise interactions with other members of the community. Mathematically, an N-species pairwise model is:

$$\frac{dS_i}{dt} = \left(r_{i0} + \sum_{j=1}^{N} f_{ij}(S_j) \right) S_i \qquad \text{(Eq 2).}$$

Here, $f_{ij}(S_j)$ describes how S_j, the density of species $\mathbf{S_j}$, positively or negatively affects the fitness of $\mathbf{S_i}$. The pairwise additivity assumption means that $f_{ij}(S_j)$ is a linear or nonlinear function of only S_j and not of a third species. When $j=i$, $f_{ii}(S_i)$ represents intra-population density-dependent fitness effect on $\mathbf{S_i}$.

$f_{ij}(S_j)$ can have several variations (Wangersky 1978): basic Lotka-Volterra, where the fitness influence of $\mathbf{S_j}$ on $\mathbf{S_i}$ linearly increases with the abundance of $\mathbf{S_j}$ (Solé and Bascompte 2006); logistic Lotka-Volterra, which considers resource limitation by specifying a carrying capacity for each species (Thébault and Fontaine 2010; Mougi and Kondoh 2012); Lotka-Volterra with delayed influence, where the fitness influence of one species on another may lag in time (Gopalsamy 1992), and saturable Lotka-Volterra, where the fitness effect of $\mathbf{S_j}$ on $\mathbf{S_i}$ saturates at high density of $\mathbf{S_j}$ (Thébault and Fontaine 2010). Since we model continuous growth which does not impose carrying

capacity and since chemical influence from one species to another is likely saturable, we have adopted the saturable Lotka-Volterra as our canonical pairwise model:

$$\frac{dS_i}{dt} = \left[r_{i0} + \sum_j r_{ij} \frac{S_j}{S_j + K_{ij}} \right] S_i \qquad \text{(Eq 3).}$$

Here, r_{ij} is the maximal positive or negative fitness effect of S_j on S_i, and K_{ij} is the S_j exerting half maximal fitness influence on S_i (parameter definition in Fig 1 table). When $j=i$, nonzero r_{ii} and K_{ii} reflect density-dependent growth effect in S_i (e.g. inhibition or stimulation of g rowth at high cell densities).

From a mechanistic model, we derive a pairwise model either analytically or numerically (Fig 2A). In the latter case (Fig 2B-C), we should already have a pre-specified pairwise model (e.g. the canonical pairwise model) in mind. We then use the mechanistic model dynamics of monocultures and pairwise cocultures to find parameters that minimize the difference between the two models in a training time window T. Specifically, we define a distance measure $\tilde{D}$ as the fold-difference between the dynamics from the two models, averaged over a time interval τ and species number N (Fig 2C):

$$\tilde{D} = \frac{1}{N} \sum_{i=1}^{N} \left[\frac{1}{\tau} \int_\tau D_i(t) dt \right] = \frac{1}{N} \sum_{i=1}^{N} \left[\frac{1}{\tau} \int_\tau \left| \log_{10} \left(S_{i,pair}(t) / S_{i,mech}(t) \right) \right| dt \right] \qquad \text{(Eq 4)}$$

where $S_{i,pair}$ and $S_{i,mech}$ are S_i calculated using pairwise and mechanistic models, respectively. Since species with densities below a set extinction limit, S_{ext}, are assumed to have gone extinct in the model, we set all densities below the extinction limit to S_{ext} in calculating $\tilde{D}$ to avoid singularities. Within the training window T, minimizing $\tilde{D}$ using a nonlinear least square routine yields parameters of the best-matching pairwise model. We then use $\tilde{D}$ outside the training window to quantify how well the best-matching pairwise model predicts the mechanistic model.

Reusable and consumable mediators are best represented by different forms of pairwise models

To build a pairwise model, we must accurately represent the fitness influence of one species on another (r_{ij} and K_{ij}). Even though this basic process seems straightforward as outlined in Fig 2, in practice, challenges may arise. For example, identifying the set of best-matching parameters for nonlinear functions may not be straightforward, and measurement errors further hamper parameter estimation. Partly due to these challenges, studies on deriving pairwise model parameters for a given community are scarce (Pascual and Kareiva 1996; Stein et al. 2013), despite the popularity of pairwise models. In this section, we analytically derive pairwise models from mechanistic models of two-species communities where one species affects the other species through a single mediator. The mediator is either reusable such as signaling molecules in quorum sensing (Duan et al. 2009; N.S. Jakubovics 2010) or consumable such as metabolites (Stams 1994; Freilich et al. 2011). We show that a single canonical pairwise model may not encompass these different interaction mechanisms.

Consider a commensal community where species $\mathbf{S_1}$ stimulates the growth of species $\mathbf{S_2}$ by producing a reusable (Fig 3A) or a consumable chemical $\mathbf{C_1}$ (Fig 3B). When $\mathbf{C_1}$ is reusable, the mechanistic model can be transformed into a pairwise model (Fig 3A), provided that the concentration of the mediator (which is initially zero) has acclimated to be proportional to the producer population size (Fig 3A; Fig3-FS1). This pairwise model takes the canonical form (compare with Fig 1B right). Thus, the canonical pairwise model is appropriate, regardless of whether the producer coexists with the consumer, outcompetes the consumer, or is outcompeted by the consumer.

If $\mathbf{C_1}$ is consumable, different scenarios are possible: when $\mathbf{C_1}$ is consumed slowly compared to production, it will accumulate within each dilution cycle without plateauing to a steady state (Fig 3-FS2 left panel, similar to a reusable mediator in Fig3-FS1A). In this case, $\mathbf{C_1}$ may be approximated as a reusable mediator and can be predicted by the canonical pairwise model (Fig 3-FS2 right panel, compare dotted and solid lines). We will henceforward classify these accumulating consumable mediators also as reusable.

If within each dilution cycle after an initial period of time, $\mathbf{C_1}$ approximately reaches a steady state (i.e., $dC_1/dt \sim 0$; Fig3-FS3), we can mathematically eliminate C_1. The resultant equation below differs from the canonical pairwise model:

$$\frac{dS_2}{dt} = r_{20}S_2 + \frac{S_1}{\omega S_1 + \psi S_2} S_2 \qquad \text{(Eq 5)}$$

where ω and ψ are constants (Fig 3B-ii; Fig 3-Supplementary Text (a)). This alternative pairwise model computed from the mechanistic model predicts community dynamics reasonably well, even if the initial species composition is not at steady state (Fig 3-FS3, compare dashed and solid lines). To estimate parameters of the alternative pairwise model, acclimation time to reach steady state is required (Fig 3-FS4 bottom panels, less accurate estimation of r_{21} compared to analytically calculated r_{analyt} before reaching steady state). Moreover, a gentler dilution scheme better fulfills the steady state approximation, and therefore leads to a closer match between the estimated and analytically calculated parameter values (Fig 3-FS4). The alternative pairwise model, suitable for steady state $\mathbf{C_1}$, is not predictive of community dynamics where $\mathbf{C_1}$ accumulates without reaching a steady state (Fig 3-FS2, compare dashed and solid lines).

An interaction mediated by a consumable mediator that reaches steady state usually cannot be described by a canonical model (Fig 3-Supplementary Text (b)). This is because parameters estimated at the steady state can predict steady state (Fig 3-FS3A), but not when initial species ratios differ from the steady state ratio (Fig 3-FS3B and C, compare dotted with solid lines). In contrast, the alternative model (Fig 3-FS3, dashed lines) provides a much better approximation.

The alternative model can be further simplified if additionally, the half-saturation constant ***K*** for **C₁** consumption ($K_{C_1S_2}$) is identical to that for **C₁**'s influence on the growth of consumer ($K_{S_2C_1}$) (the "***K*** assumption"), so long as $S_2>0$ (Fig 3B-iii). This equation form has precedence in the literature (e.g. (Mougi and Kondoh 2012)), where the interaction strength r_{21} reflects the fact that the consumable mediator from S_1 is divided among consumer S_2.

If C_1 is consumable but eventually declines to zero concentration (e.g. when consumer outcompetes producer), then estimating the interaction coefficient r_{21} for the canonical or the alternative pairwise model can be difficult (Fig 3-FS5).

We have shown here that even when one species affects another species via a single mediator, depending on whether the mediator is reusable or consumable and whether it accumulates or reaches a steady state, a canonical or an alternative form of pairwise model is appropriate. Neither model is effective when the consumable mediator concentration declines to zero, although this problem could be mitigated by setting up the measurements properly. Considering that reusable and consumable mediators are both common, our results call for revisiting the universality assumption of pairwise modeling.

Multi-mediator interactions require pairwise models different from single-mediator interactions

A species often affects another species via multiple mediators (Kato et al. 2008; Traxler et al. 2013; Kim, Lee, and Ryu 2013). For example, a subpopulation from one species might die and release numerous chemicals that can affect another species in different ways. Here we examine cases where S_1 releases two chemicals C_1 and C_2 which additively affect the growth of S_2 (Fig 4). We ask when two mediators can mathematically be regarded as one mediator (to facilitate further abstraction into a pairwise model) and how multi-mediator interactions affect pairwise modeling.

When both mediators are reusable (Fig 4-Supplementary Text), their combined effect ($\frac{r_{S_2C_1}S_1}{S_1+K_{S_2C_1}r_{10}/\beta_{C_1S_1}}+\frac{r_{S_2C_2}S_1}{S_1+K_{S_2C_2}r_{10}/\beta_{C_2S_1}}$) generally cannot be modeled as a single mediator except under special conditions (Fig 4). These special conditions include: (1) mediators share similar "potency" (Fig 4C, diagonal), or (2) one mediator has much stronger "potency" than the other (i.e. one mediator dominates the interaction; note the log scale in Fig 4C).

When both mediators are consumable and eventually reach steady state, the interaction term becomes $\frac{S_1}{\omega_{C_1}S_1+\psi_{C_1}S_2}+\frac{S_1}{\omega_{C_2}S_1+\psi_{C_2}S_2}$. Except under special conditions (e.g. when both mediators satisfy the ***K*** assumption in Fig 3B-iii, or when $\omega_{C_1}/\omega_{C_2}=\psi_{C_1}/\psi_{C_2}$, or when one mediator dominates the interaction), the two mediators may not be regarded as one. Similarly,

when one mediator is a steady-state consumable and the other is reusable, they generally may not be regarded as a single mediator and would require yet a different pairwise model with more degrees of freedom (with the interaction term $\frac{S_1}{\omega_{C_1} S_1 + \psi_{C_1} S_2} + \frac{r_{S_2 C_2} S_1}{S_1 + K_{S_2 C_2} r_{10} / \beta_{C_2 S_1}}$). All these forms deviate from the canonical form.

In summary, when $\mathbf{S_1}$ influences $\mathbf{S_2}$ through multiple mediators, rarely can we approximate them as a single mediator. Multiple mediators generally make equations of pairwise modeling more complex than single mediators, casting further doubt on the usefulness of a universal form for all community interactions.

A multispecies pairwise model can work for interaction chains but generally not for interaction modifications

For a community with more than two species, can we construct a multispecies pairwise model from two-species pairwise models? The answer is yes for an interaction chain mediated by chemicals (Fig 5A), so long as mediators between different species pairs are independent and each species pair can be represented by a pairwise model. The equation form of the multispecies pairwise model can vary, depending on whether the mediator is consumable or reusable (Fig 5-Supplementary Text).

As known from previous work (Fig 1-Supplementary Text), interaction modification can cause a multispecies pairwise model to fail. For example, $\mathbf{S_1}$ releases $\mathbf{C_1}$ which stimulates $\mathbf{S_2}$ growth; $\mathbf{C_1}$ is consumed by $\mathbf{S_3}$ and stimulates $\mathbf{S_3}$ growth (Fig 5C). Here, the presence of $\mathbf{S_3}$ changes the strength of interaction between $\mathbf{S_1}$ and $\mathbf{S_2}$, an example of interaction modification. Viewing this differently, $\mathbf{S_1}$ changes the nature of interactions between $\mathbf{S_2}$ and $\mathbf{S_3}$: $\mathbf{S_2}$ and $\mathbf{S_3}$ do not interact in the absence of $\mathbf{S_1}$, but $\mathbf{S_3}$ inhibits $\mathbf{S_2}$ in the presence of $\mathbf{S_1}$. This causes pairwise modeling to make qualitatively wrong conclusions about species persistence (Fig 5D). As expected, if $\mathbf{S_3}$ does not remove $\mathbf{C_1}$, the three-species pairwise model works (Fig 5-FS1, A-B).

Interaction modification can occur even in communities where no species changes "the nature of interactions" between any other two species (Fig 5E). Here, both $\mathbf{S_1}$ and $\mathbf{S_3}$ contribute reusable $\mathbf{C_1}$ to stimulate $\mathbf{S_2}$. $\mathbf{S_1}$ promotes $\mathbf{S_2}$ regardless of $\mathbf{S_3}$; $\mathbf{S_3}$ promotes $\mathbf{S_2}$ regardless of $\mathbf{S_1}$; $\mathbf{S_1}$ and $\mathbf{S_3}$ do not interact regardless of $\mathbf{S_2}$. However, a multispecies pairwise model assumes that the fitness effects from the two producers on $\mathbf{S_2}$ will be additive, whereas in reality, the fitness effect on $\mathbf{S_2}$ saturates at high C_1. As a result, even though the dynamics of each species pair can be represented by a pairwise model (Fig 5F right, purple), the three-species pairwise model fails to capture community dynamics (Fig 5F). Thus, the nonlinearity in how a mediator affects a species can also violate the additivity assumption of a pairwise model. As expected, if $\mathbf{C_1}$ affects $\mathbf{S_2}$ in a linear fashion, the community dynamics is accurately captured in the multispecies pairwise model (Fig 5-FS1, C-D).

In summary, for chemical-mediated indirect interactions, a multispecies pairwise model can work for the interaction chain category but generally not the mediator modification category.

Discussion

Multispecies pairwise models are widely used in theoretical research due to their simplicity. In two-species interactions such as prey-predation based on contact-dependent inhibition (instead of diffusible chemical mediators), Lotka-Volterra pairwise models can in fact be the mechanistic representation of interactions and thus predictive of community dynamics (Fig 1-FS1). The inadequacy of multispecies pairwise models has been discussed theoretically (Wootton 2002; Wootton and Emmerson 2005) and empirically (Case and Bender 1981; Dormann and Roxburgh 2005; Aschehoug and Callaway 2015), although the reasons for model failures in explaining experimental results are often unclear (Billick and Case 1994).

Here, we have considered the validity of pairwise models in well-mixed two- and three-species communities where all species interactions in a community are known and thus community dynamics can be described by a mechanistic reference model. We have focused on chemical-mediated interactions commonly encountered in microbial communities (Fig 1-FS2) (Kato et al. 2005; Gause 1934a; Ghuysen 1991; Nicholas S Jakubovics et al. 2008; Chen et al. 2004; D'Onofrio et al. 2010; Johnson et al. 1982; Hamilton and Ng 1983). To favor the odds of successful pairwise modeling, we have also assumed that different chemical mediators exert additive fitness effects on a target species.

What are the conditions under which the influence of one species on another can be represented by a canonical two-species pairwise model (the universality assumption)? When an interaction employs a single mediator, then a canonical saturable pairwise model (Fig 1B) will work for a reusable mediator (Fig 3A) but generally not for a consumable mediator that fails to accumulate throughout each dilution cycle (Fig 3 Supplement Text (b); Fig 3-FS5). Instead, an alternative pairwise model is suited for a consumable mediator that reaches steady state (Fig 3B, Fig 3-FS3). If one species influences another through multiple mediators, then in general, these mediators may not be regarded as a single mediator and conditions for a working canonical pairwise model become even more restrictive (Fig 4 and Fig 4-Supplementary Text).

In communities of more than two species, indirect interactions via a third species can occur. For indirect interactions via interaction chain, as long as each two-species segment of the chain engages in independent interactions and can be represented by a pairwise model, then multispecies pairwise models will generally work (Figs 5A-B, Fig 5-Supplementary Text). However, depending on whether each mediator is reusable or not, equation forms will vary. For indirect interactions via interaction modification (higher-order interactions), even if each species pair can be accurately represented by a pairwise model, a multispecies pairwise model may fail (Fig 5, C-F). Interaction modification includes trait modification (Wootton 2002; Werner and Peacor 2003; Schmitz,

Krivan, and Ovadia 2004), or, in our cases, mediator modification. Mediator modification is very common in microbial communities. For example, antibiotic released by one species to inhibit another species may be inactivated by a third species, and this type of indirect interactions can stabilize microbial communities (Kelsic et al. 2015). Moreover, interaction mediators are often shared among multiple species. For example in oral biofilms, organic acids such as lactic acid are generated from carbohydrate fermentation by many species (Bradshaw et al. 1994; Marsh and Bradshaw 1997; Kuramitsu et al. 2007). Such by-products are also consumed by multiple species (Kolenbrander 2000).

Pairwise modeling (or variations of it) still has its uses when simulating a particular community phenomenologically. One can even imagine that an extended pairwise model (e.g. $\frac{dS_2}{dt} = r_{20}S_2 + \frac{S_1}{\varsigma + \omega S_1 + \psi S_2} S_2$) embodying both the canonical form and the alternative form (Fig 3) can serve as a general-purpose model for pairwise interactions via a single mediator. Even the effects of indirect interactions may be quantified and included in the model by incorporating higher-order interaction terms (Case and Bender 1981; Worthen and Moore 1991), although many challenges will need to be overcome (Wootton 2002). In the end, although these strategies may lead to a sufficiently accurate phenomenological model for specific cases, "one-form-fitting-all" may generate erroneous predictions when modeling different communities.

How much information about interaction mechanisms do we need to construct a mechanistic model? That is, what is the proper level of abstraction which captures the phenomena of interest, yet avoids unnecessary details (Levins 1966; Durrett and Levin 1994; Damore and Gore 2012)? Tilman argued that if a small number of mechanisms (e.g. the "axes of trade-offs" in species' physiological, morphological, or behavioral traits) could explain much of the observed pattern (e.g. species coexistence), then this abstraction would be highly revealing (Tilman 1987). However, the choice of abstraction is often not obvious. Consider for example a commensal community where $\mathbf{S_1}$ grows exponentially (not explicitly depicted in equations in Fig 6) and the growth rate of $\mathbf{S_2}$, which is normally zero, is promoted by mediator **C** from $\mathbf{S_1}$ in a linear fashion (Fig 6). If we do not know how $\mathbf{S_1}$ stimulates $\mathbf{S_2}$, we can still construct a pairwise model (Fig 6A). If we know the identity of mediator **C** and realize that **C** is consumable, then we can instead construct a mechanistic model incorporating $\boldsymbol{C}$ (Fig 6B). However, if **C** is produced from a precursor via an enzyme **E** released by $\mathbf{S_1}$, then we get a different form of mechanistic model (Fig 6C). If, on the other hand, **E** is anchored on the membrane of $\mathbf{S_1}$ and each cell expresses a similar amount of **E**, then equations in Fig 6D are mathematically equivalent to Fig 6B. This simple example, inspired by extracellular breakdown of cellulose into a consumable sugar **C** (Bayer and Lamed 1986; Felix and Ljungdahl 1993; Schwarz 2001)), illustrates how knowledge of mechanisms may eventually help us determine the right level of abstraction.

In summary, under certain circumstances, we may already know that interaction mechanisms fall within the domain of validity for a pairwise model. In these cases, pairwise modeling provides the appropriate level of abstraction, and constructing a pairwise model can be far easier than measuring the many parameters required by a mechanistic model. However, if we do not know whether pairwise modeling is valid, we will need to be cautious about indiscriminative use of pairwise models since they can fail to even qualitatively capture community dynamics (e.g. Fig3-FS2, Fig3-FS3, Fig 5C-F). We will need to be equally careful in extrapolating and generalizing conclusions obtained from pairwise models. Considering recent advances in identifying and quantifying interactions, we advocate a transition to models that incorporate interaction mechanisms at the appropriate level of abstraction.

Methods

Simulations are based on Matlab® and executed on an ordinary PC. The following list describes the m-files used for different steps of the analysis:

File name	**Function**
FitCost_BasalFitness	Calculates the cost function for monocultures (i.e. the difference between the target dynamics and the dynamics obtained from the pairwise model)
Fitcost_BFSatLV.m	Calculates the cost function for communities (i.e. the difference between the target dynamics and the dynamics obtained from the pairwise model)
DynamicsMM_WM_MonocultureDpMM.m	Returns the dynamics of growth for monocultures, based on the mechanistic model
DynamicsMM_WM_NetworkDpMM.m	Returns the dynamics of growth for communities of multiple species, based on the mechanistic model
DynamicsWM_NetworkBFSatLV.m	Returns the dynamics of growth for communities of multiple species, based on the canonical pairwise model
DynamicsWM_NetworkBFSatLV_Dp.m	Returns the dynamics of growth for communities of multiple species, based on the alternative pairwise model
DeriveBasalFitnessMM_WM_DpMM.m	Estimates the basal fitness of species by finding the model parameters of monocultures that best fit the dynamics obtained from the mechanistic model
DeriveBFSatLVMM_WM_DpMM.m	Estimates the interaction strengths by finding the canonical pairwise model parameters of communities that best fit the dynamics obtained from the mechanistic model
DeriveBFSatLVMM_WM_DpMM_Dp.m	Estimates the interaction strengths by finding the alternative pairwise model parameters of communities that best fit the dynamics obtained from the mechanistic model
DeriveBFSatLVMM_WM_DpMM_r21.m	Estimates $\boldsymbol{r_{21}}$ and $\boldsymbol{K_{21}}$ of a canonical pairwise model to best fit the dynamics obtained from the mechanistic model (used in cases where we know only $\mathbf{S_2}$ is affected by $\mathbf{S_1}$ to accelerate the optimization)
DeriveBFSatLVMM_WM_DpMM_Dp_r21.m	Estimates $\boldsymbol{r_{21}}$ of an alternative pairwise model to best fit the dynamics obtained from the mechanistic model (used in

	cases where we know only $\mathbf{S_2}$ is affected by $\mathbf{S_1}$ to accelerate the optimization)

Fitting is performed using nonlinear least square (lsqnonlin routine) with default optimization parameters.

Steps:

1. Fit monoculture data to find r_{i0}, r_{ii}, and K_{ii}
2. Fit coculture data with pairs to find r_{ij}, r_{ji}, and K_{ij} and K_{ji}
3. Calculate distance between population dynamics of the reference mechanistic model and the approximate pairwise model over several generations outside of the training window to assess if the pairwise model is predictive

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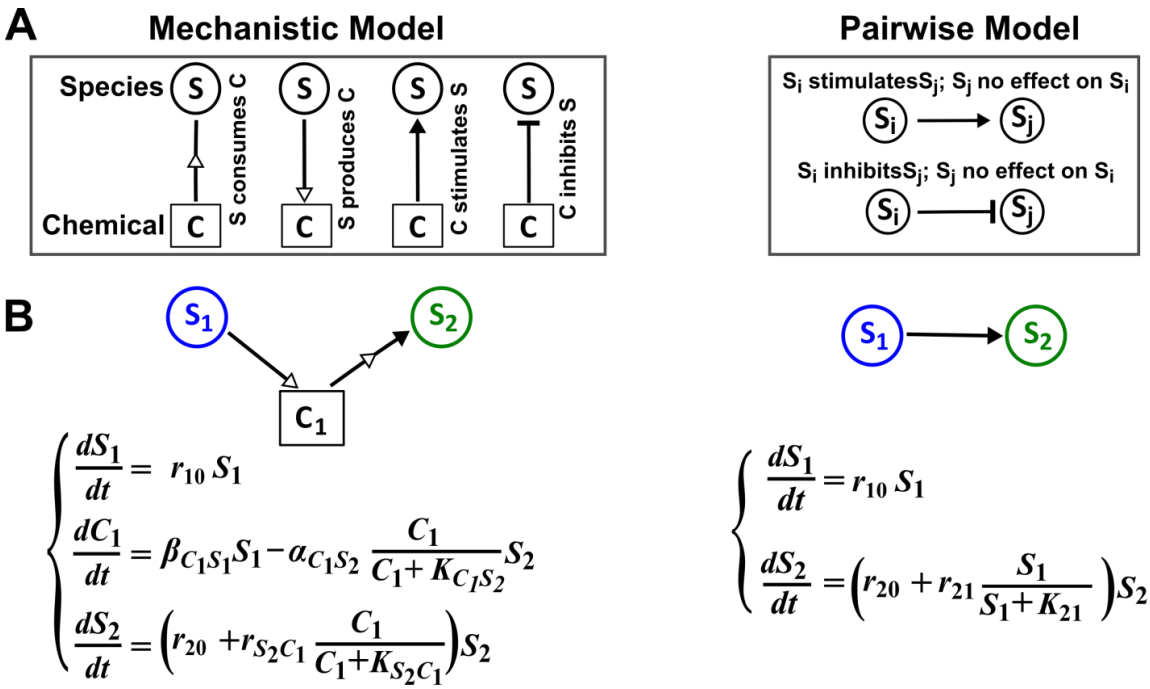
Figures



$$\begin{cases} \dfrac{dS_1}{dt} = r_{10} S_1 \\ \dfrac{dC_1}{dt} = \beta_{C_1 S_1} S_1 - \alpha_{C_1 S_2} \dfrac{C_1}{C_1 + K_{C_1 S_2}} S_2 \\ \dfrac{dS_2}{dt} = \left(r_{20} + r_{S_2 C_1} \dfrac{C_1}{C_1 + K_{S_2 C_1}} \right) S_2 \end{cases}$$

$$\begin{cases} \dfrac{dS_1}{dt} = r_{10} S_1 \\ \dfrac{dS_2}{dt} = \left(r_{20} + r_{21} \dfrac{S_1}{S_1 + K_{21}} \right) S_2 \end{cases}$$

		Description	Mech.	Pair.
state variable	S_1 & S_2	population density of species S_1 and S_2	✓	✓
	C_1	chemical C1 concentration	✓	
parameter	r_{10} & r_{20}	basal growth rate of S_1 and S_2 in the absence of interactions	✓	✓
	$\beta_{C_1 S_1}$	production rate of C_1 by S_1	✓	
	$\alpha_{C_1 S_2}$	max consumption rate of C_1 by S_2	✓	
	$K_{C_1 S_2}$	C_1 conc. at which S_2 consumes C_1 at half max rate	✓	
	$r_{S_2 C_1}$; $K_{S_2 C_1}$	max strength and half saturation conc. of C_1 influence on S_2	✓	
	r_{21} & K_{21}	max strength and half saturation conc. of S_1 influence on S_2		✓

Fig 1. The abstraction of interaction mechanisms in a pairwise model compared to a mechanistic model.

(**A**) The mechanistic model (left) considers a bipartite network of species and chemical interaction mediators. A species can produce or consume chemicals (open arrowheads pointing towards and away from the chemical, respectively). A chemical mediator can positively or negatively influence the fitness of its target species (filled arrowhead and bar, respectively). The corresponding pairwise model (right) includes only the fitness effects of species on themselves and other species, which can be positive (filled arrowhead), negative (bar), or zero (line terminus). (**B**) In the example here, species $\mathbf{S_1}$ releases chemical $\mathbf{C_1}$, and $\mathbf{C_1}$ is consumed by species $\mathbf{S_2}$ and promotes $\mathbf{S_2}$'s fitness. In the mechanistic model, the three equations respectively state that 1) $\mathbf{S_1}$ grows exponentially at a rate r_{10}, 2) $\mathbf{C_1}$ is released by $\mathbf{S_1}$ at a rate $\beta_{C_1 S_1}$ and

consumed by $\mathbf{S_2}$ with saturable kinetics, and 3) $\mathbf{S_2}$'s growth (basal fitness $\boldsymbol{r_{20}}$) is influenced by $\boldsymbol{C_1}$ in a saturable fashion. In the pairwise model here, the first equation is identical to that of the mechanistic model. The second equation is similar to the last equation of the mechanistic model except that $\boldsymbol{r_{21}}$ and $\boldsymbol{K_{21}}$ together reflect how the density of $\mathbf{S_1}$ ($\boldsymbol{S_1}$) affects the fitness of $\mathbf{S_2}$ in a saturable fashion. For all parameters with double subscripts, the first subscript denotes the focal species or chemical, and the second subscript denotes the influencer. Note that unlike in mechanistic models, we have omitted "$\boldsymbol{S}$" from subscripts in pairwise models (e.g. $\boldsymbol{r_{21}}$ instead of $\boldsymbol{r}_{S_2 S_1}$) for simplicity.

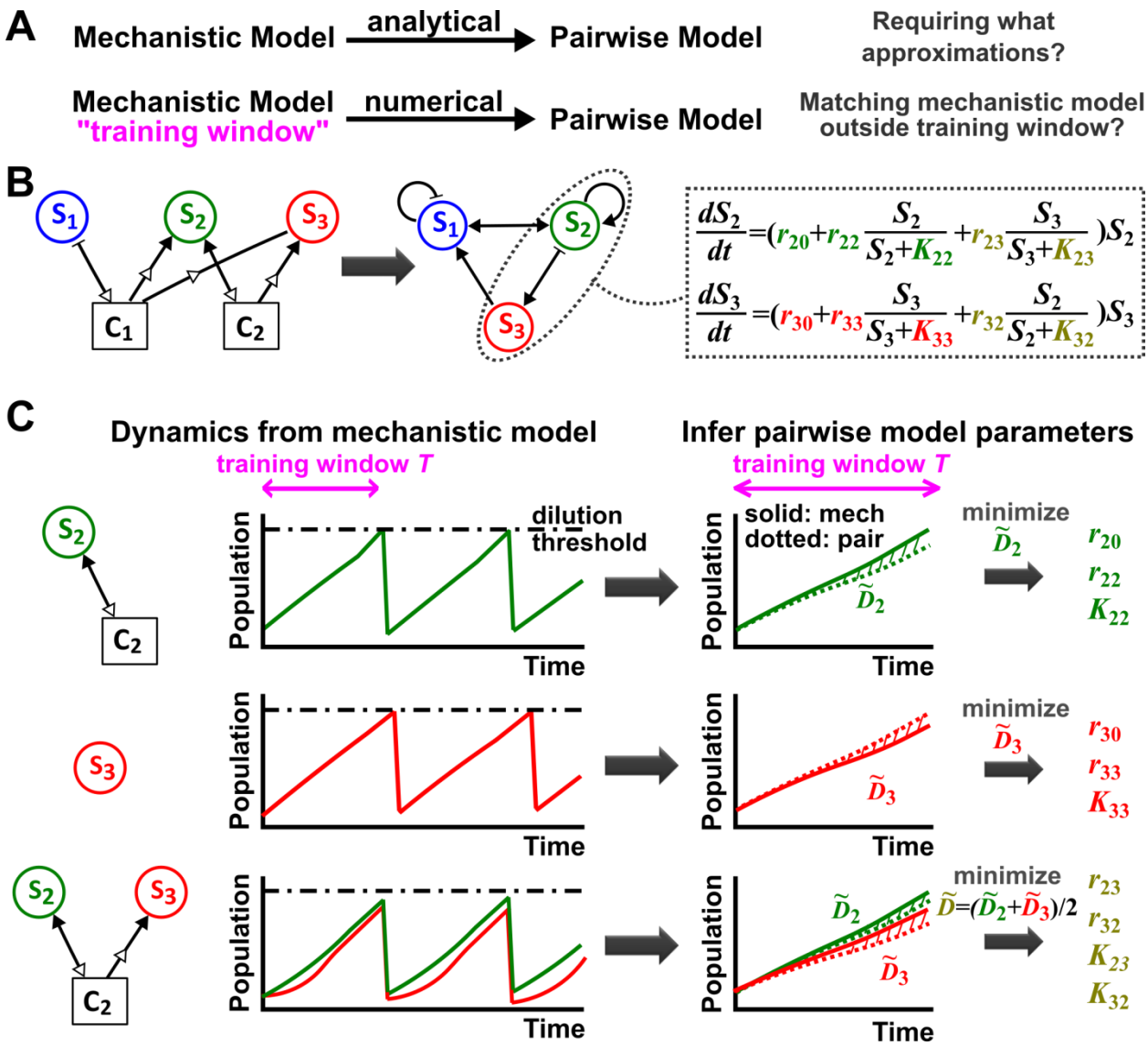


Fig 2. Deriving a pairwise model.

(**A**) Analytically deriving a pairwise model from a mechanistic model allows us to uncover approximations required for such a transformation (top). Alternatively (bottom), through a "training window" of the mechanistic model population dynamics, we can numerically derive parameters for a pre-selected pairwise model that best fits the mechanistic model. We then quantify how well such a pairwise model matches the mechanistic model under conditions different from those of the training window. (**B**) A mechanistic model of three species interacting via two chemicals (left) can be translated into a pairwise model of three interacting species (center). $\mathbf{S_1}$ inhibits $\mathbf{S_1}$ and promotes $\mathbf{S_2}$ (via $\mathbf{C_1}$). $\mathbf{S_2}$ promotes $\mathbf{S_2}$ and $\mathbf{S_3}$ (via $\mathbf{C_2}$) as well as $\mathbf{S_1}$ (via removal of $\mathbf{C_1}$). $\mathbf{S_3}$ promotes $\mathbf{S_1}$ and inhibits $\mathbf{S_2}$ (via removal of $\mathbf{C_1}$ and $\mathbf{C_2}$, respectively). Take interactions between $\mathbf{S_2}$ and $\mathbf{S_3}$ for example: the saturable Lotka-Volterra pairwise model will require estimating ten parameters (colored, right), some of which (e.g. r_{33} in this case) may be zero. (**C**) In the numerical method, the six monoculture parameters (r_{i0}, r_{ii}, and K_{ii}, i=2, 3; green and red) are first estimated from training window T (within a dilution cycle) of monoculture mechanistic models. Subsequently, the four parameters representing interspecies interactions (r_{ij} and K_{ij}, $i \neq j$, olive) can be estimated from the

training window $\boldsymbol{T}$ of the $\boldsymbol{S_2 + S_3}$ coculture mechanistic model. Parameter definitions are described in Fig 1. In all simulations, to ensure that resources not involved in interactions are never limiting, a community is diluted back to its inoculation density when total population increases to a high-density threshold. To estimate parameters, we use an optimization routine to minimize $\tilde{\boldsymbol{D}}$, the fold-difference (shaded area) between dynamics from a pairwise model (dotted lines) and the mechanistic model (solid lines) averaged over $\boldsymbol{T}$. Too frequent dilutions will allow only small changes in population dynamics within a dilution cycle or $\boldsymbol{T}$, which is not suitable for estimating pairwise models. Too infrequent dilutions will cause large fluctuations in dynamics, which is not ideal for pairwise models based on steady-state assumptions (Fig 3-FS4). Under most cases, dilution frequency does not affect our conclusions.

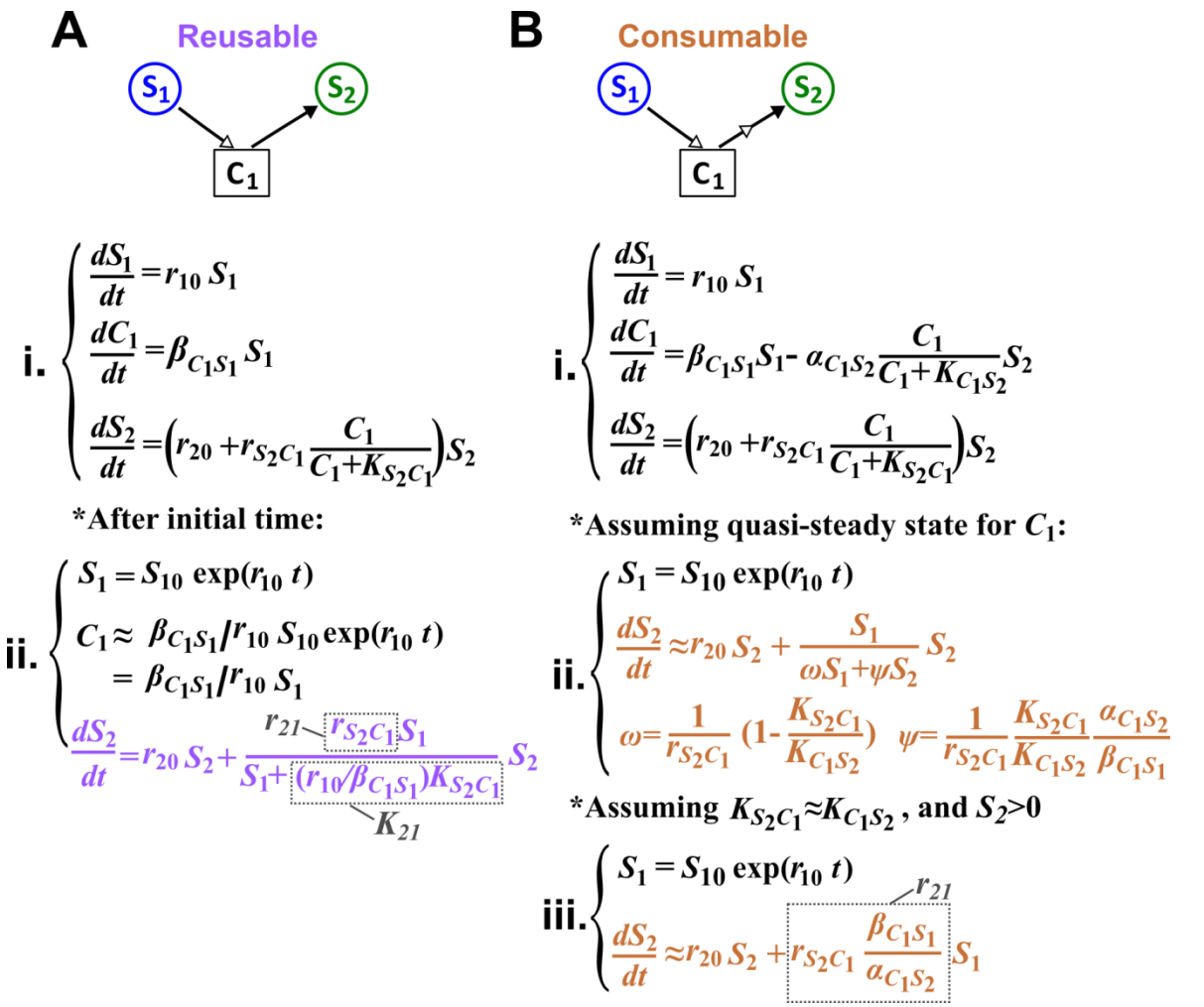


Fig 3. Interactions mediated via a single reusable or consumable mediator are best represented by different forms of pairwise models.

$\mathbf{S_1}$ stimulates the growth of $\mathbf{S_2}$ via a reusable (**A**) or a consumable (**B**) chemical $\mathbf{C_1}$. In mechanistic models of the two cases, equations for S_1 and S_2 are identical but equations for C_1 are different. In (**A**), C_1 can be solved to yield $C_1 = (\beta_{C_1S_1}/r_{10})S_{10}\exp(r_{10}t) - (\beta_{C_1S_1}/r_{10})S_{10} = (\beta_{C_1S_1}/r_{10})S_1 - (\beta_{C_1S_1}/r_{10})S_{10}$ assuming zero initial C_1. We have approximated C_1 by omitting the second term (valid after the initial transient response has passed so that C_1 has become proportional to S_1). This approximation allows an exact match between the canonical pairwise model (Fig 1B right) and the mechanistic model (ii), and thus justifies the pairwise model. In (**B**), assuming quasi-steady state C_1 (negligible dC_1/dt), we can solve and eliminate C_1 (ii). Assuming that K_{C1S2} (C_1 for half maximal consumption rate by $\mathbf{S_2}$) is identical to K_{S2C1} (C_1 for half maximal stimulation of $\mathbf{S_2}$ growth) and S_2>0, we can further simplify the pairwise model (iii). Thus, depending on whether the mediator is consumed or reused, the most appropriate pairwise model (colored) takes different forms. Pairwise model parameters (r_{21} and K_{21}) are marked within grey boxes.

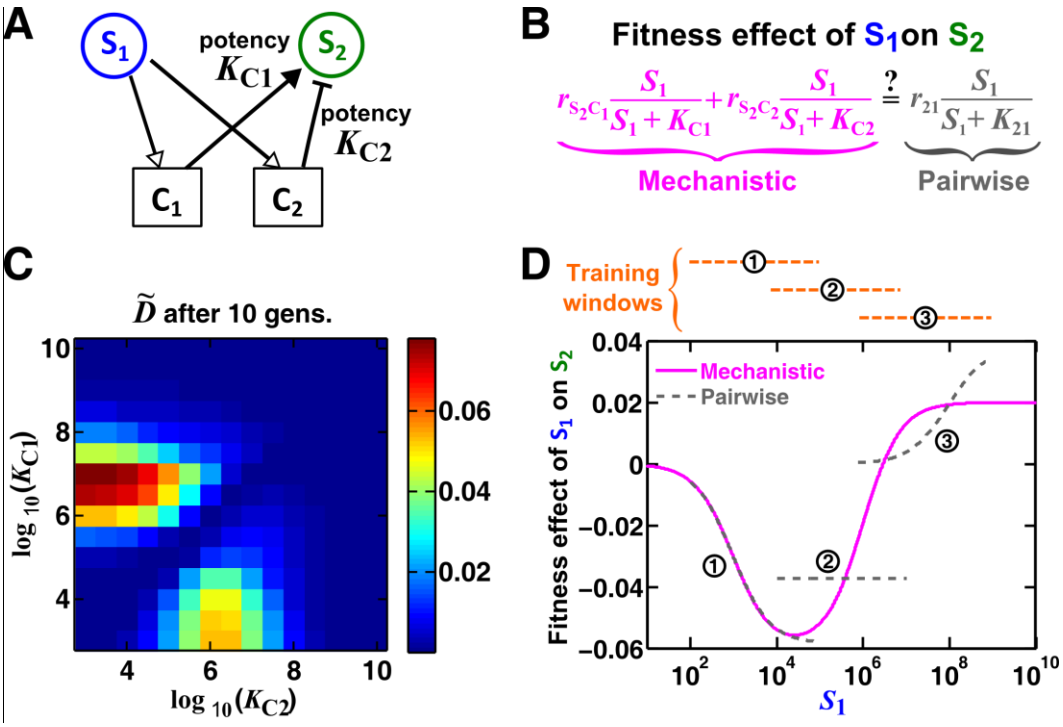


Fig 4. A pairwise model often fails when one species affects another via multiple reusable mediators.

(**A**) One species can affect another species via two reusable mediators, each with a different potency K_{Ci} where K_{Ci} is $K_{S_2C_i}\, r_{10}/\beta_{C_iS_1}$ (Fig 4-Supplementary Text). A low K_{Ci} indicates a strong potency (e.g. high release of C_i by S_1 or low C_i required to achieve half-maximal influence on S_2). (**B**) Under what conditions can an interaction via two reusable mediators be approximated by a pairwise model? (**C**) Under restricted conditions, two reusable mediators can be consolidated into a single mediator. We can directly compute the best-fitting pairwise model parameters over a training window of T by minimizing $\tilde{D}$ (Fig 4-Supplementary Text, Eq 4S-2). Here, the difference $\tilde{D}$ between the two models over T =10 generations is plotted over a range of potencies K_{C1} and K_{C2}. Using the canonical pairwise model is valid (blue regions indicating small difference) when $K_{C1} \approx K_{C2}$ or when one interaction is orders of magnitude stronger than the other interaction (Fig 4-Supplementary Text). (**D**) A community where the canonical pairwise model is not valid. Here, $K_{C1}=10^3$ and $K_{C2}=10^6$. We estimate the best-fitting pairwise model by minimizing $\tilde{D}$ (Fig 4-Supplementary Text, Eq 4S-2) in three training windows (spanning 10 generations of growth for S_1). At various S_1, we calculate the fitness effect of S_1 on S_2 using the pairwise model and the mechanistic model (**B**). In two of the three training windows, the two models fail to match. In the training window with the lowest S_1, the two models match because the effect of C_2 is negligible in this range ($K_{C2} >> S_1$, condition iib in Fig 4-Supplementary Text). These mismatches mean that a pairwise model cannot consistently capture reference dynamics. Simulation parameters are listed in Fig 4-SD1.

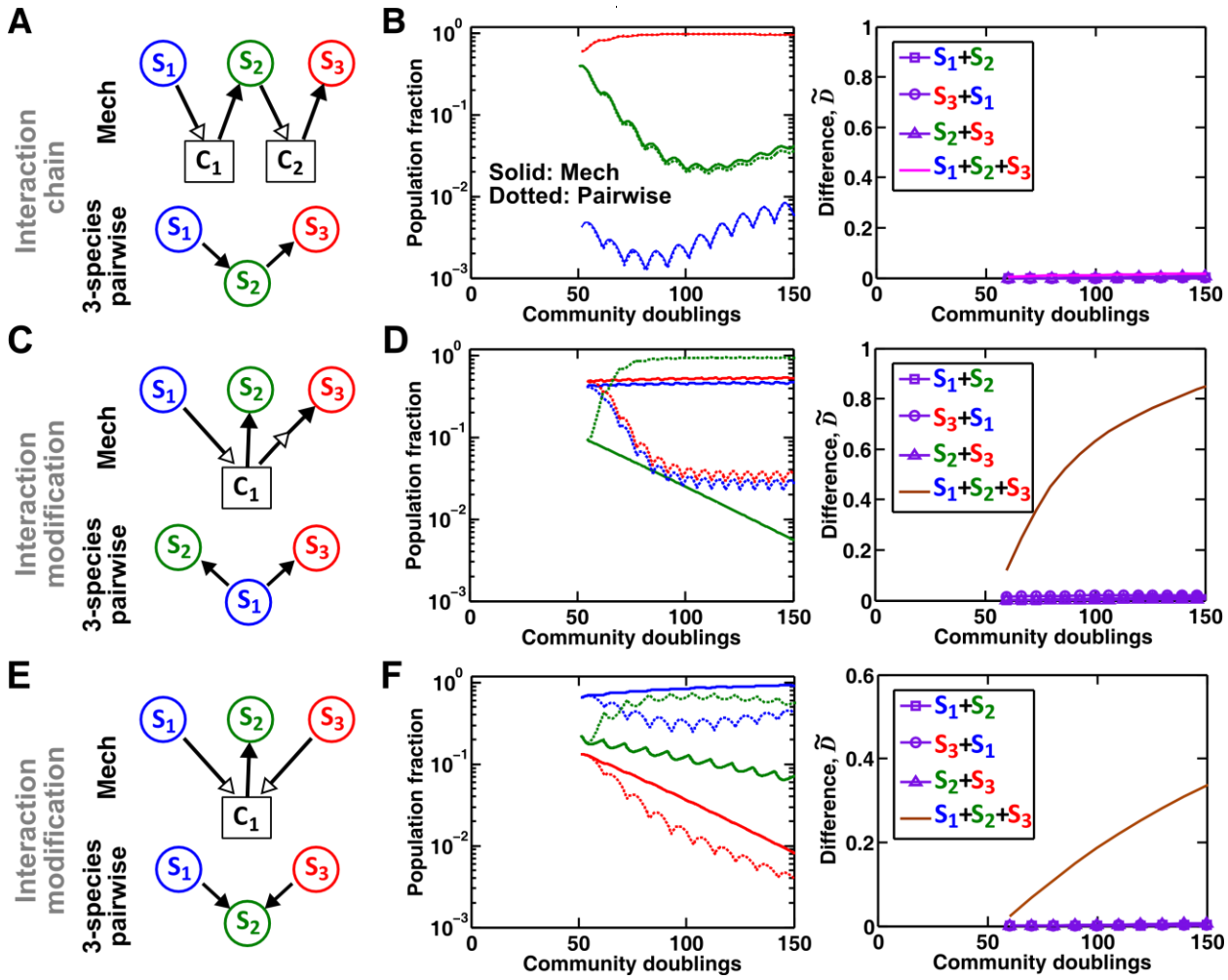


Fig 5. Interaction chain but not interaction modification may be represented by a pairwise model. We examine three-species communities engaging in indirect interactions. Each species pair is representable by a two-species pairwise model (purple in the right columns of **B**, **D,** and **F**). We then use these two-species pairwise models to construct a three-species pairwise model, and test how well it predicts the dynamics from mechanistic model. In **B**, **D**, and **F**, left panels show dynamics from the mechanistic models (solid lines) and three-species pairwise models (dotted lines). Right panels show the difference metric $\tilde{D}$ calculated over population densities after taking dilution into consideration. (**A-B**) Interaction chain: $\mathbf{S_1}$ affects $\mathbf{S_2}$, and $\mathbf{S_2}$ affects $\mathbf{S_3}$. The two interactions employ independent mediators $\mathbf{C_1}$ and $\mathbf{C_2}$, and both interactions can be represented by the canonical pairwise model. The three-species pairwise model matches the mechanistic model in this case. Simulation parameters are provided in Fig 5-SD1. (**C-F**) Interaction modification. (**C-D**) $\mathbf{S_3}$ consumes $\mathbf{C_1}$, a mediator of interaction exerted on $\mathbf{S_2}$ by $\mathbf{S_1}$. Parameters are listed in Fig 5-SD2. (**E-F**) $\mathbf{S_1}$ and $\mathbf{S_3}$ both supply $\mathbf{C_1}$ which stimulates $\mathbf{S_2}$. Simulation parameters are listed in Fig 5-SD3. In both interaction modification cases, the three-species pairwise model fails to predict reference dynamics.

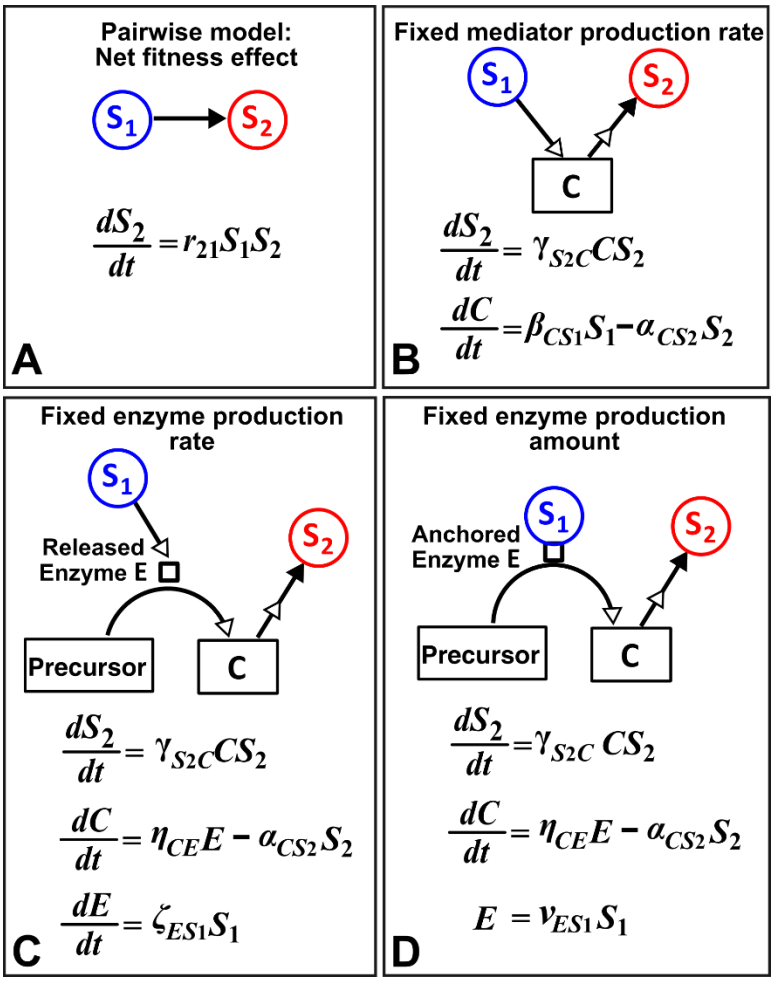


Fig 6. Different levels of abstraction in mechanistic modeling.

How one species (S_1) may influence another (S_2) can be mechanistically modeled at different levels of abstraction. For simplicity, here we assume that interaction strength scales in a linear (instead of saturable) fashion with respect to mediator concentration or species density. The basal fitness of S_2 is zero. (**A**) In the simplest form, S_1 stimulates S_2 in a pairwise model. (**B**) In a mechanistic model, we may realize that S_1 stimulates S_2 via a mediator **C** which is consumed by S_2. The corresponding mechanistic model is given. (**C**) Upon probing more deeply, it may become clear that S_1 stimulates S_2 via an enzyme **E**, where **E** degrades an abundant precursor (such as cellulose) to generate mediator **C** (such as glucose). In the corresponding mechanistic model, we may assume that **E** is released by S_1 at a rate ζ_{ES1} and that **E** liberates **C** at a rate η_{CE}. (**D**) If instead **E** is anchored on the cell surface (e.g. in cellulose degradation via cellulosome), then E is proportional to S_1. If we substitute E into the second equation, then **(B)** and **(D)** become equivalent. Thus, when enzyme is anchored on cell surface but not when enzyme is released, the mechanistic knowledge of enzyme can be neglected.

Supplementary figures

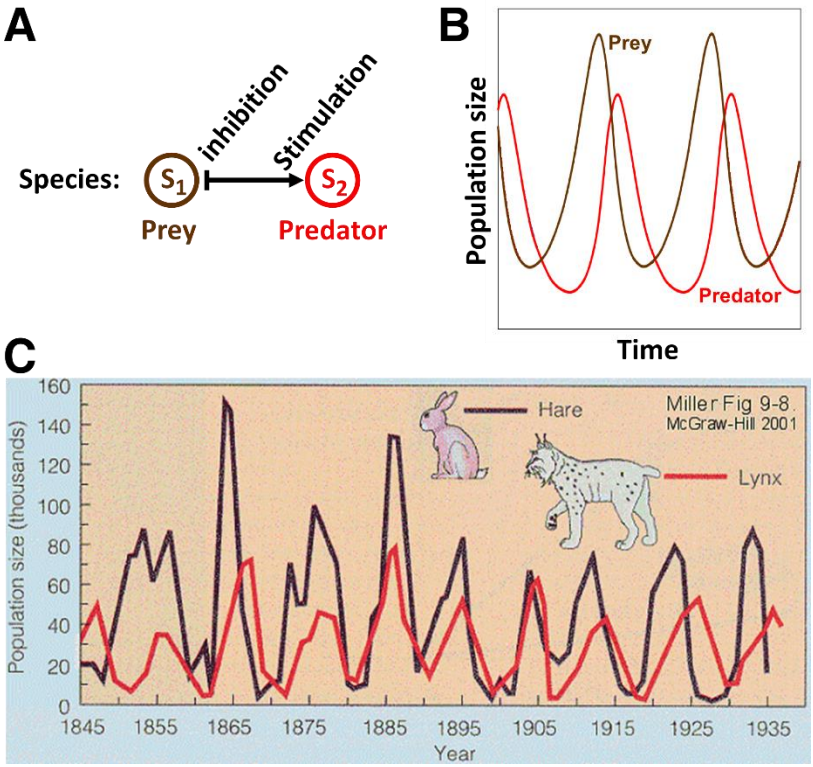


Fig 1-FS1. A pairwise model successfully predicts oscillations in population dynamics of the hare-lynx prey-predator community.

(**A**) In a pairwise model of prey-predation proposed by Lotka and Volterra, predator reduces the fitness of prey, while prey stimulates the fitness of predator. (**B**) Assuming random encounter between prey and predator, the pairwise model predicts oscillations in the prey and predator population sizes. (**C**) Similar oscillations have been qualitatively observed in natural populations of lynx and hare, providing support for the usefulness of pairwise modeling. Picture is reproduced from ("BiologyEOC - PopulationChanges" 2016).

Fig 1-Supplementary Text. Interaction modification but not interaction chain violates the pairwise additivity assumption

In a pairwise model, the fitness of a focal species $\mathbf{S_i}$ is the sum of its "basal fitness" (r_{i0}, the net growth rate of a single individual in the absence of any intra-species or inter-species interactions) and the additive fitness effects exerted by pairwise interactions with other members of the community. Mathematically, an N-species pairwise model is often formulated as

$$\frac{dS_i}{dt} = \left(r_{i0} + \sum_{j=1}^{N} f_{ij}(S_j) \right) S_i \qquad \text{(Eq S1-1; Eq 2 in the main text).}$$

Here, $f_{ij}(S_j)$ describes how S_j, the density of species $\mathbf{S_j}$, positively or negatively affects the fitness of $\mathbf{S_i}$, and is a linear or nonlinear function of only S_j and not of a third species.

Indirect interactions via a third species fall under two categories (Wootton 1993). The first type is known as "interaction chain" or "density-mediated indirect interactions". For example, the consumption of plant $\mathbf{S_1}$ by herbivore $\mathbf{S_2}$ is reduced when the density of herbivore is reduced by carnivore $\mathbf{S_3}$. In this case, the three-species pairwise model

$$\begin{cases} \frac{dS_1}{dt} = \left(r_{10} - f_{12}(S_2)\right) S_1 \\ \frac{dS_2}{dt} = \left(r_{20} + f_{21}(S_1) - f_{23}(S_3)\right) S_2 \\ \frac{dS_3}{dt} = \left(r_{30} + f_{32}(S_2)\right) S_3 \end{cases} \qquad \text{(Eq S1-2)}$$

does not violate the pairwise additivity assumption (Case and Bender 1981; Wootton 1994) (compare with Eq S1-1).

The second type of indirect interactions is known as "interaction modification" or "trait-mediated indirect interactions" or "higher order interactions" (Vandermeer 1969; Wootton 1994; Billick and Case 1994; Wootton 2002), where a third species modifies the "nature of interaction" from one species to another (Wootton 2002; Werner and Peacor 2003; Schmitz, Krivan, and Ovadia 2004). For example, when carnivore is present, herbivore will spend less time foraging and consequently plant density increases. In this case, f_{12} in Eq S1-2 is a function of both S_2 and S_3, violating the pairwise additivity assumption.

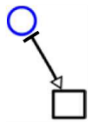
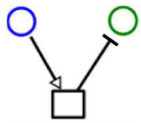
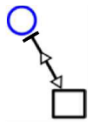
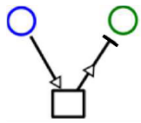
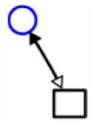
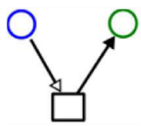
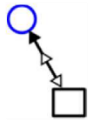
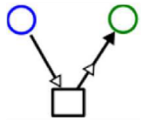
Interaction		Type	Example
Intrapopulation	Interpopulation		
		Target cell not degrading its inhibitor	Accumulation of waste products such as acetate (Kato et al. 2005) or ethanol (Gause, 1934a)
		Target cell degrading its inhibitor	β-lactamase degrading penicillin (Ghuysen 1991) Catalase neutralizing H_2O_2 (Jakubovics et al. 2008)
		Target cell not consuming its activator	Quorum sensing (Chen et al. 2004) Growth-promoting factors (D'Onofrio et al. 2010)
		Target cell consuming its activator	Producing saccharides (via cellulose digestion), and consuming saccharides (Johnson et al. 1982) By-product commensalism (Hamilton and Ng 1983)

Fig 1-FS2. Chemical-mediated interactions commonly found in microbial communities.
Interactions can be intra- or inter-population. Examples are meant to be illustrative instead of comprehensive.

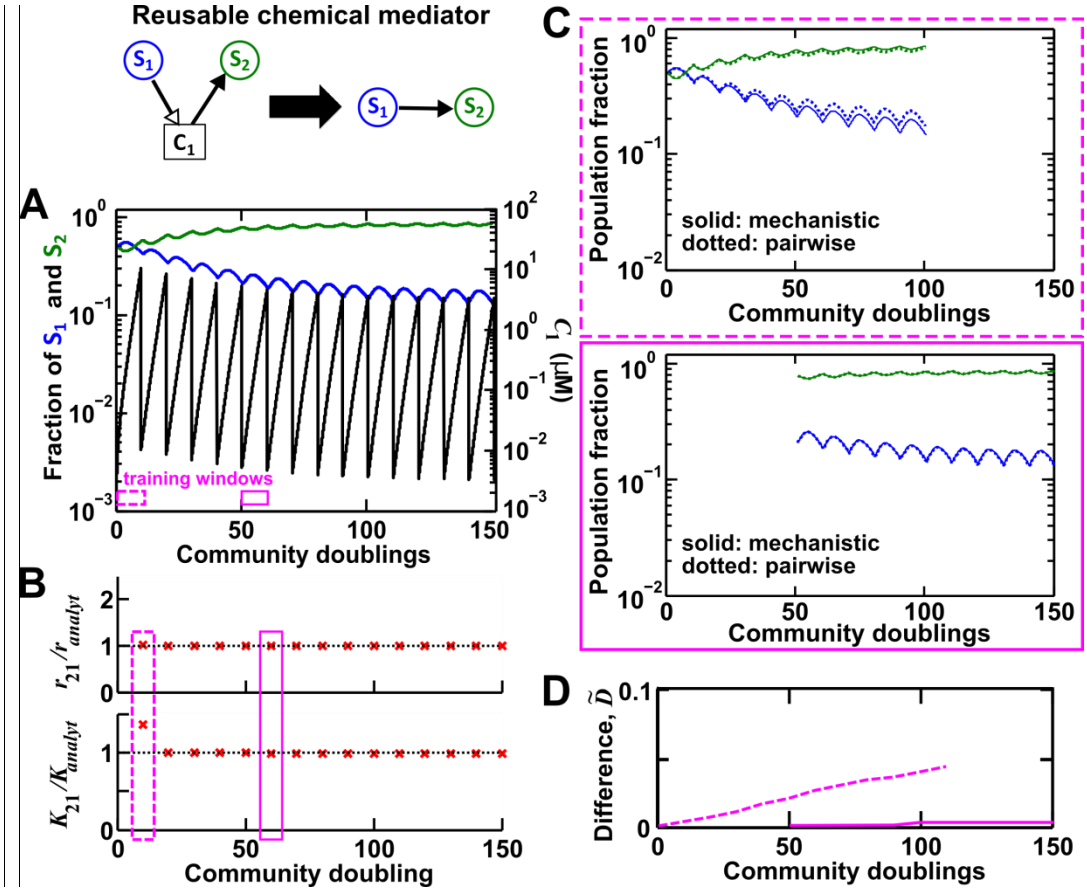


Fig 3-FS1. For a reusable mediator, parameter estimation after acclimation time leads to a more accurate canonical pairwise model.

(**A**) We use the mechanistic model for a reusable mediator to generate reference dynamics of S_1, S_2, and C_1 over 150 generations of community growth. The basal fitness of S_1 and S_2 in pairwise models are identical to those in mechanistic models, and here r_{ii} or K_{ii} (i = 1, 2) are irrelevant due to the lack of intra-population interactions. We use every 10 community doublings of reference dynamics as training windows to numerically estimate best-matching canonical pairwise model parameters r_{21} and K_{21}. Dashed and solid rectangles represent training windows before and after acclimation, respectively. Note that population fractions (instead of population densities) are plotted, which fluctuate less during dilutions compared to mediator concentration. (**B**) Pairwise model parameters estimated after acclimation (solid rectangle) match their analytically-derived counterparts (black dotted lines) better than those estimated before acclimation (dashed rectangle). (**C**) A pairwise model generated from population dynamics before acclimation (top) predicts future reference dynamics less accurately than that generated after acclimation (bottom). (**D**) Quantification of the difference between pairwise and mechanistic models before (dashed) or after (solid) acclimation. All parameters are listed in Fig 3-SD1.

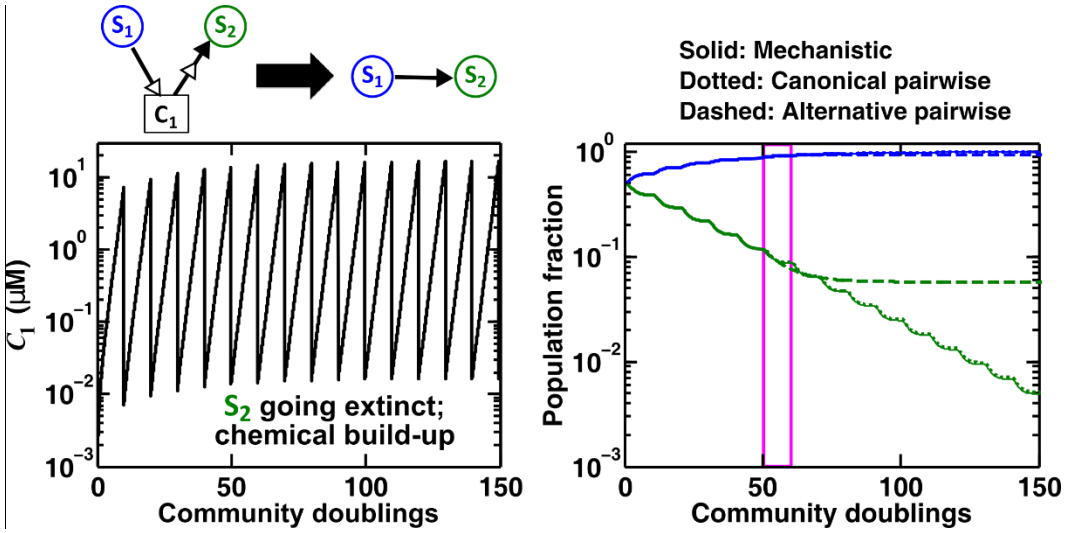


Fig 3-FS2. A canonical pairwise model, but not the alternative pairwise model, is suitable for a consumable mediator that accumulates without reaching a steady state within each dilution cycle. In a commensal community, the consumable mediator $\mathbf{C_1}$ accumulates as the consumer $\mathbf{S_2}$ gradually goes extinct. Pairwise model parameters are estimated from the mechanistic model dynamics in the training window (magenta, between 50 and 60 generations). The canonical model (Fig 3A) shows dynamics (dotted) that match those of the mechanistic model (solid). As expected, the alternative pairwise model (Fig 3B), which assumes steady state C_1, fails (dashed). Thus, accumulating $\mathbf{C_1}$ can be regarded as a reusable mediator. Note that population fractions (instead of population densities) are plotted, which fluctuate less during dilutions compared to mediator concentration. All parameters are listed in Fig 3-SD4.

Fig 3-Supplementary Text. An alternative form of pairwise model best represents interactions mediated by a single consumable mediator that reaches a non-zero steady-state.

(a) Deriving an alternative pairwise model

From Fig 3B, the mechanistic model is

$$\begin{cases} \dfrac{dS_1}{dt} = r_{10}S_1 \\ \dfrac{dS_2}{dt} = r_{20}S_2 + r_{S_2C_1}\dfrac{C_1}{C_1 + K_{S_2C_1}}S_2 \\ \dfrac{dC_1}{dt} = \beta_{C_1S_1}S_1 - \alpha_{C_1S_2}\dfrac{C_1}{C_1 + K_{C_1S_2}}S_2 \end{cases}$$

Under the quasi-steady state assumption ($dC_1/dt \approx 0$), we obtain

$$\beta_{C_1S_1}S_1 = \alpha_{C_1S_2}\frac{C_{1,ss}}{C_{1,ss} + K_{C_1S_2}}S_2 \qquad \text{(Eq 3S-1)}$$

or

$$C_{1,ss} = \frac{\beta_{C_1S_1}S_1}{\alpha_{C_1S_2}S_2 - \beta_{C_1S_1}S_1}K_{C_1S_2} \qquad \text{(Eq 3S-2)}$$

where $C_{1,ss}$ is the steady state level of C_1.

From Eq 3S-1, $S_1/S_2 = \dfrac{\alpha_{C_1S_2}}{\beta_{C_1S_1}}\dfrac{C_{1,ss}}{C_{1,ss} + K_{C_1S_2}}$ is a constant, which means that the two species should grow at the same rate (in this case, r_{10}).

If C_1 has not yet reached steady state, assuming steady state C_1 and accepting its consequence of constant S_1/S_2 would falsely predict S_1/S_2 remaining at the initial value (Fig3-FS3, dotted lines). However, if we do not insist S_1/S_2 being a constant, we obtain an alternative pairwise model:

$$\frac{dS_2}{dt} = r_{20}S_2 + r_{S_2C_1}\frac{\beta_{C_1S_1}K_{C_1S_2}S_1}{\beta_{C_1S_1}(K_{C_1S_2} - K_{S_2C_1})S_1 + \alpha_{C_1S_2}K_{S_2C_1}S_2}S_2 \qquad \text{(Eq 3S-3a)}$$

or

$$\frac{dS_2}{dt} = r_{20}S_2 + \frac{S_1}{\omega S_1 + \psi S_2}S_2 \qquad \text{(Eq 3S-3b)}$$

where ω and ψ are constants.

This alternative model makes reasonable predictions of community dynamics even before the community reaches the steady state (Fig 3-FS3, compare dashed and solid lines). This is because the alternative model allows the community dynamics to always change towards the steady-state. To see this, we note that at steady-state, the two species grow at the same rate, i.e.

$$r_{10} = r_{20} + \frac{S_{1,ss}}{\omega S_{1,ss} + \psi S_{2,ss}} \quad \text{or} \quad r_{10} - r_{20} = \frac{\left(S_1/S_2\right)_{ss}}{\omega\left(S_1/S_2\right)_{ss} + \psi}.$$

Starting from a non-steady-state initial ratio, the growth rate of $\mathbf{S_2}$ will be

$$r_2 = r_{20} + \frac{S_1}{\omega S_1 + \psi S_2} = r_{20} + \frac{\left(S_1/S_2\right)}{\omega\left(S_1/S_2\right) + \psi}$$

To compare whether $\mathbf{S_2}$ is growing faster or slower than $\mathbf{S_1}$, we can calculate

$$\Delta r = r_2 - r_1 = r_{20} + \frac{\left(S_1/S_2\right)}{\omega\left(S_1/S_2\right) + \psi} - r_{10}.$$

Since $r_{10} - r_{20} = \frac{\left(S_1/S_2\right)_{ss}}{\omega\left(S_1/S_2\right)_{ss} + \psi}$, we get

$$\Delta r = \frac{\left(S_1/S_2\right)}{\omega\left(S_1/S_2\right) + \psi} - \frac{\left(S_1/S_2\right)_{ss}}{\omega\left(S_1/S_2\right)_{ss} + \psi}$$

The function $f(x) = \frac{x}{\omega x + \psi}$ monotonically increases with x since $\psi > 0$, thus

$$\begin{cases} \Delta r = r_2 - r_1 > 0 & \textit{when } \left(S_1/S_2\right) > \left(S_1/S_2\right)_{ss} \\ \Delta r = r_2 - r_1 < 0 & \textit{when } \left(S_1/S_2\right) < \left(S_1/S_2\right)_{ss} \end{cases}.$$

This means that $\mathbf{S_2}$ grows faster (slower) than $\mathbf{S_1}$ when S_1/S_2 is greater (smaller) than the steady state value.

(b) Failure of canonical pairwise model

If we were to estimate parameters of a canonical pairwise model for such a community at steady state $C_{1,ss}$ and $(S_1/S_2)_{ss}$, we would change Eq 3S-3b to:

$$\frac{dS_2}{dt} = r_{20} S_2 + \frac{S_{1,ss}}{\omega S_{1,ss} + \psi S_{2,ss}} \frac{S_1}{S_1 + K_{21}} S_2 \qquad \text{(Eq 3S-4)}$$

where $K_{21} << S_1$, and $r_{21} = \frac{(S_1/S_2)_{ss}}{\omega(S_1/S_2)_{ss} + \psi}$

This leads to erroneous predictions when initial ratios are not at steady-state (Fig 3-FS3 B, C).

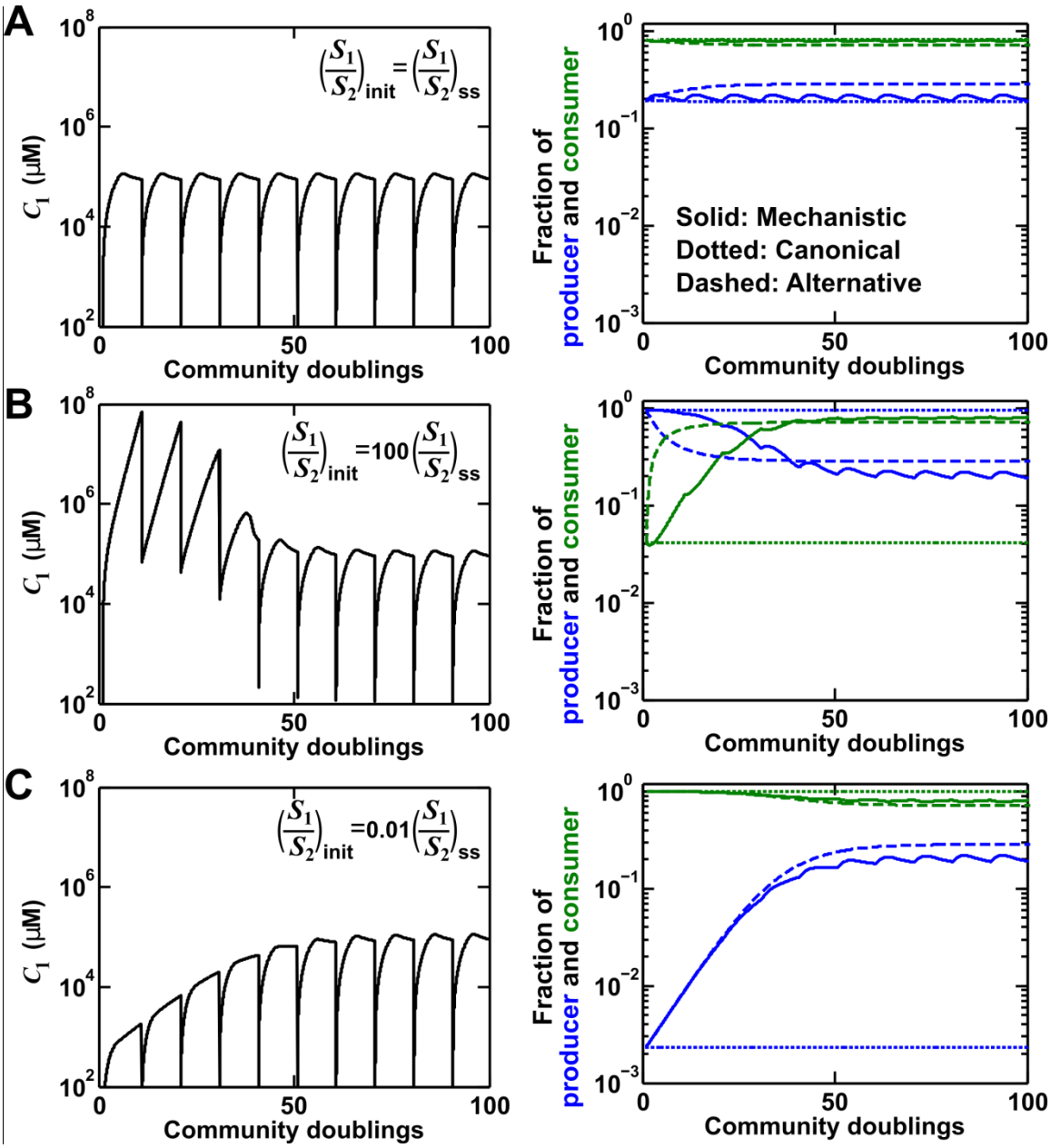


Fig 3-FS3. Interactions mediated through a consumable chemical that reaches a pseudo-steady state can be represented by the alternative but not canonical pairwise model.

Consider a commensal interaction where the consumable mediator reaches a non-zero steady state. We directly compute from the mechanistic model the corresponding canonical pairwise model (Fig 3-Supplementary Text (b), Eq 3S-4 with the assumption of steady state S_1/S_2) or alternative pairwise model (Fig 3B). (**A**) As expected, when the community starts at the steady state, both the canonical and the alternative pairwise models predict steady-state dynamics. (**B** and **C**) When the community does not start at the steady state, the canonical model falsely predicts the maintenance of initial ratios. The alternative model predicts a convergence to the steady state, similar to the mechanistic reference model. Note that population fractions (instead of population densities) are plotted, which fluctuate less during dilutions compared to mediator concentration. All parameters are listed in Fig 3-SD3.

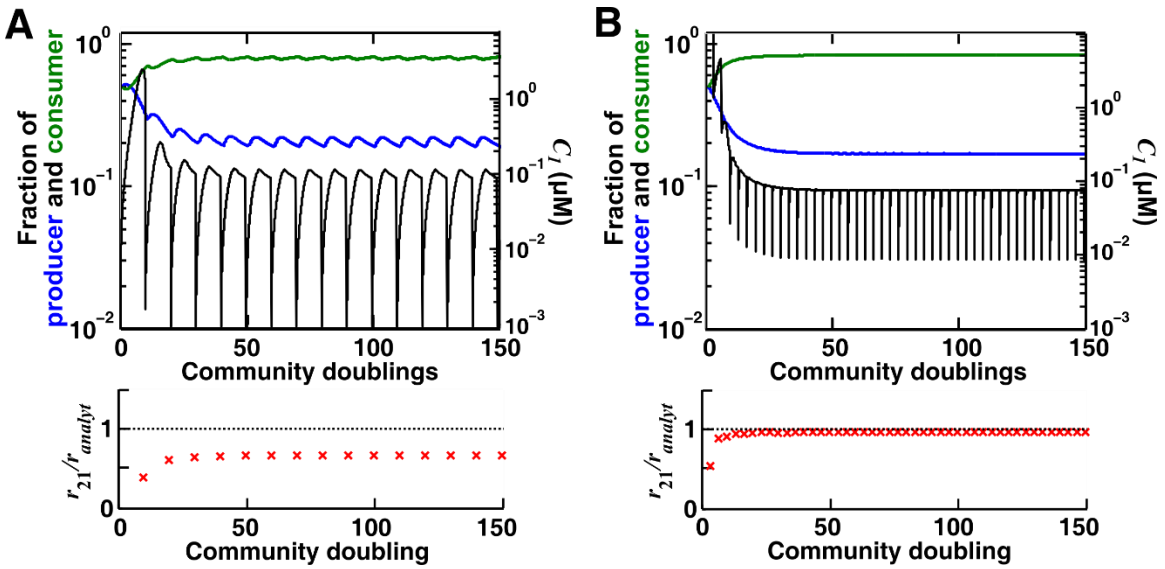


Fig 3-FS4. The degree of validity of the quasi-steady state assumption influences the accuracy of parameter estimation for the alternative pairwise model.

We consider commensalism through a consumable mediator, where the producer (blue) and the consumer (green) eventually reach a steady state. We compare 1000-fold (**A**) and 10-fold (**B**) dilution steps to examine how fluctuations caused by dilutions affect parameter estimation. We use every 10 community doublings of reference dynamics as training windows to numerically estimate best-matching alternative pairwise model parameters. In (**A**), compared to (**B**), we see larger errors in estimating the interaction strength r_{21} compared to the true value (calculated from Fig 3B). In both (**A**) and (**B**), parameter estimations are less accurate if estimated before (instead of after) the steady state has been reached. Note that population fractions (instead of population densities) are plotted, which fluctuate less during dilutions compared to mediator concentration. All parameters are listed in Fig 3-SD5.

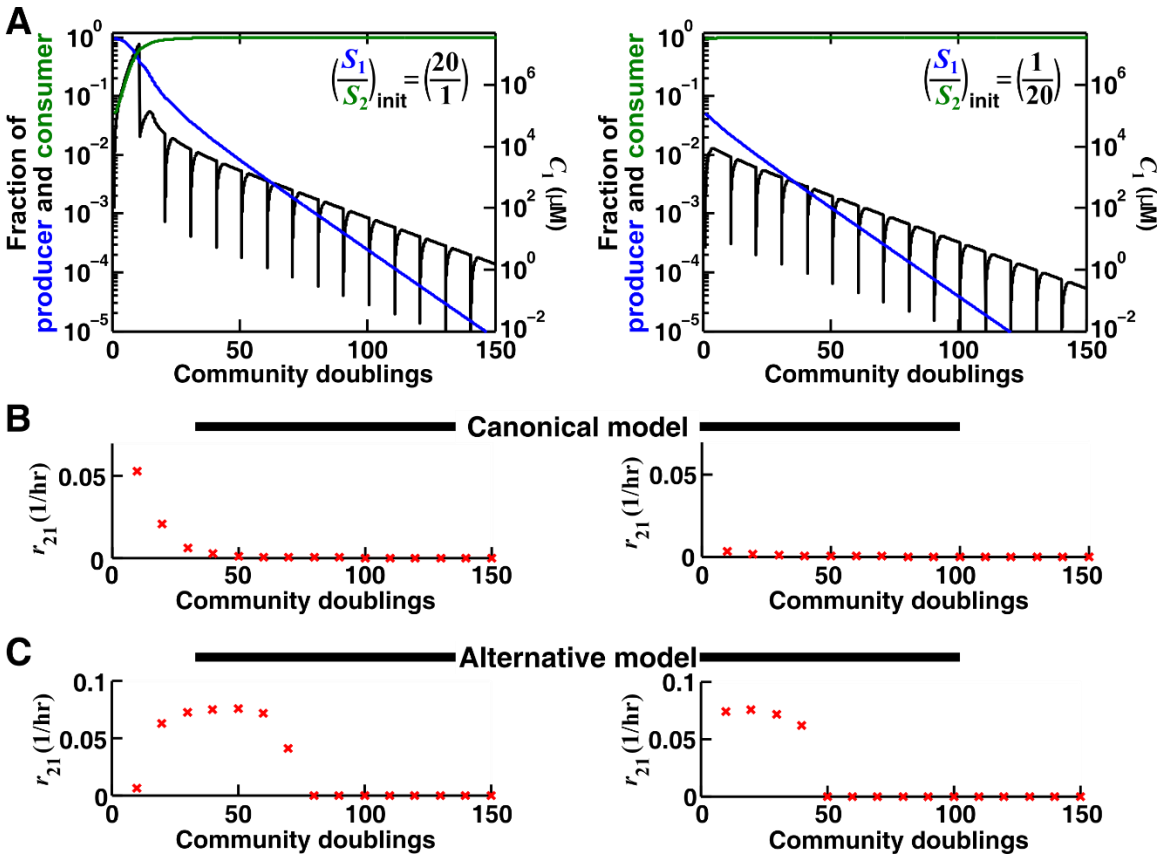


Fig 3-FS5. Inconsistent pairwise model parameters if a consumable mediator declines to zero. Consider a community where $\mathbf{S_1}$ (blue) produces a mediator that is consumed by $\mathbf{S_2}$ (green) and that stimulates the growth of $\mathbf{S_2}$. Suppose that the basal fitness of $\mathbf{S_1}$ is lower than that of $\mathbf{S_2}$, then $\mathbf{S_1}$ will go extinct. Community dynamics at two different initial species ratios are shown (**A**). Note that population fractions (instead of population densities) are plotted, which fluctuate less during dilutions compared to mediator concentration. (**B**) and (**C**) respectively show parameter estimates for the canonical (Fig 3A) versus the alternative (Fig 3B) pairwise model, using training windows of ten generations. When initial $\boldsymbol{S_1/S_2}$ is 20, the mediator initially accumulates due to the scarcity of consumers (**A**, left panel). Interaction coefficient r_{21} estimated from the canonical model is initially strong, but rapidly approaches zero (**B**, left panel). The alternative model is not suitable for the first ten generations due to mediator accumulation. After the first ten generations, the alternative model predicts a relatively consistent interaction coefficient due to the slowly-declining mediator concentration which can be approximated as a non-zero steady state. However, r_{21} approaches zero as the ratio of producer to consumer drops to very low values (**C**, left panel). (**B-C**, right panels) Similar failure at an initial $\boldsymbol{S_1/S_2}$ of 1/20. All parameters are listed in Fig 3-SD6.

Fig 4-Supplementary Text. Conditions under which a pairwise model can represent one species influencing another via two reusable mediators.

Here, we examine a simple case where $\mathbf{S_1}$ releases reusable $\mathbf{C_1}$ and $\mathbf{C_2}$, and $\mathbf{C_1}$ and $\mathbf{C_2}$ additively affect the growth of $\mathbf{S_2}$ (see example in Fig 4).

The mechanistic model is:

$$\begin{cases} S_1 = S_{10}\exp(r_{10}t) \\ \dfrac{dS_2}{dt} = \left(r_{20} + \dfrac{r_{S_2C_1} S_1}{S_1 + K_{S_2C_1} r_{10} / \beta_{C_1S_1}} + \dfrac{r_{S_2C_2} S_1}{S_1 + K_{S_2C_2} r_{10} / \beta_{C_2S_1}} \right) S_2 \end{cases} \qquad \text{(Eq 4S-1).}$$

Now the question is whether the canonical pairwise model

$$\begin{cases} S_1 = S_{10}\exp(r_{10}t) \\ \dfrac{dS_2}{dt} = \left(r_{20} + r_{21}\dfrac{S_1}{S_1 + K_{21}} \right) S_2 \end{cases}$$

can be a good approximation.

For simplicity, let's define $K_{C1} = K_{S_2C_1} r_{10} / \beta_{C_1S_1}$ and $K_{C2} = K_{S_2C_2} r_{10} / \beta_{C2S_1}$. Small K_{Ci} means large potency (e.g. small $K_{S_2C_2}$ which means low C_2 required to achieve half maximal effect on S_2, and/or large synthesis rate β_{C2S_1}). Since S_1 from pairwise and mechanistic models are identical, we have

$$\begin{aligned} \tilde{D} &= \frac{1}{2T}\int_T \left| \log_{10}\left(S_{2,pair}\right) - \log_{10}\left(S_{2,mech}\right) \right| dt \\ &= \frac{1}{2T\ln(10)}\int_T \left| \ln\left(S_{2,pair}\right) - \ln\left(S_{2,mech}\right) \right| dt \\ &= \frac{1}{2T\ln(10)}\int_T \left| \left(r_{20} + r_{21}\frac{S_1}{S_1 + K_{21}} \right) - \left(r_{20} + \frac{r_{S_2C_1} S_1}{S_1 + K_{C1}} + \frac{r_{S_2C_2} S_1}{S_1 + K_{C2}} \right) \right| dt \\ &= \frac{1}{2T\ln(10)}\int_T \left| r_{21}\frac{S_1}{S_1 + K_{21}} - \left(\frac{r_{S_2C_1} S_1}{S_1 + K_{C1}} + \frac{r_{S_2C_2} S_1}{S_1 + K_{C2}} \right) \right| dt \end{aligned} \qquad \text{(Eq 4S-2).}$$

$\tilde{D}$ can be close to zero when (i) $K_{C1} \approx K_{C2}$ or (ii) $\dfrac{r_{S_2C_1} S_1}{S_1 + K_{C1}}$ and $\dfrac{r_{S_2C_2} S_1}{S_1 + K_{C2}}$ (effects of $\mathbf{C_1}$ and $\mathbf{C_2}$ on $\mathbf{S_2}$) differ dramatically in magnitude. For (ii), without loss of generality, suppose that the effect of $\mathbf{C_2}$ on $\mathbf{S_2}$ can be neglected. This can be achieved if (iia) $r_{S_2C_2}$ is much smaller than $r_{S_2C_1}$, or (iib) K_{C2} is large compared to S_1.

Fig 5-Supplementary Text. A multi-species pairwise model can represent an interaction chain if each interaction can be represented by an independent pairwise model.

Without loss of generality, we show this point through an example where each step of an interaction chain is best represented by a different form of pairwise model. Suppose that $\mathbf{S_1}$ releases a reusable mediator $\mathbf{C_1}$ that promotes $\mathbf{S_2}$ and that $\mathbf{S_2}$ releases a consumable mediator $\mathbf{C_2}$ that promotes $\mathbf{S_3}$. $\mathbf{C_2}$ reaches pseudo steady-state. The corresponding community-pairwise model will be:

$$\begin{cases} \dfrac{dS_1}{dt} = r_{10} S_1 \\ \dfrac{dS_2}{dt} = \left(r_{20} + r_{21} \dfrac{S_1}{S_1 + K_{21}} \right) S_2 \\ \dfrac{dS_3}{dt} = \left(r_{30} + \dfrac{S_2}{\omega S_2 + \psi S_3} \right) S_3 \end{cases} \qquad \text{(Eq 5S-1).}$$

To see this, note that after a transient period of time, the mechanistic model of the three-species community is:

$$\begin{cases} \dfrac{dS_1}{dt} = r_{10} S_1 \\ C_1 \approx \left(\beta_{C_1 S_1} / r_{10} \right) S_1 \\ \dfrac{dS_2}{dt} = \left(r_{20} + \dfrac{r_{S_2 C_1} C_1}{C_1 + K_{S_2 C_1}} \right) S_2 = \left(r_{20} + \dfrac{r_{S_2 C_1} S_1}{S_1 + K_{S_2 C_1} r_{10} / \beta_{C_1 S_1}} \right) S_2 \\ \dfrac{dC_2}{dt} = \beta_{C_2 S_2} S_2 - \alpha_{C_2 S_3} \dfrac{C_2}{C_2 + K_{C_2 S_3}} S_3 \approx 0 \\ \dfrac{dS_3}{dt} = \left(r_{30} + r_{S_3 C_2} \dfrac{C_2}{C_2 + K_{S_3 C_2}} \right) S_3 = \left(r_{30} + \dfrac{S_2}{\omega S_2 + \psi S_3} \right) S_3 \end{cases} \qquad \text{(Eq 5S-2).}$$

Eq 5S-2 and Eq 5S-1 are equivalent.

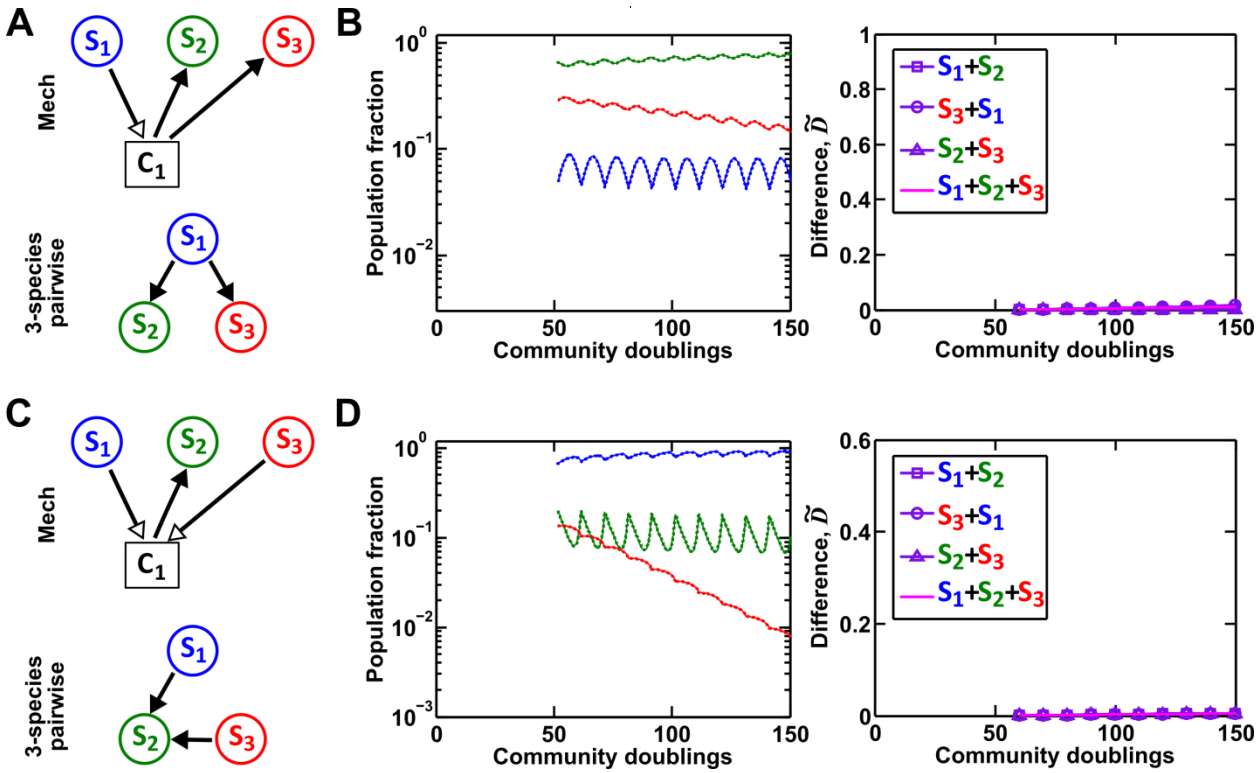


Fig 5-FS1. A multispecies pairwise model can work under special conditions.
(**A-B**) As a control for Fig 5C, if $\mathbf{S_3}$ does not remove the mediator of interaction between $\mathbf{S_1}$ and $\mathbf{S_2}$, a three-species pairwise model accurately matches the mechanistic model. Simulation parameters are provided in Fig 5-SD4. (**C-D**) As a control for Fig 5E, we ensured that fitness effects from multiple species are additive. In this case, a three-species pairwise model can represent the mechanistic model. To ensure the linearity of fitness effects, we have used a larger value of half saturation concentration ($\boldsymbol{K}_{S_2C_1} = 10^9$ instead of 10^5 in Fig 5E-F). We have adjusted the interaction coefficient accordingly such that the overall interaction strength exerted by $\mathbf{S_1}$ and $\mathbf{S_3}$ on $\mathbf{S_2}$ is comparable to that in Fig 5E-F (as evident by comparable population compositions). Since the interaction influences under these conditions remain in the linear range, the three-species pairwise model accurately predicts the reference dynamics. Simulation parameters are provided in Fig 5-SD5.