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Population–reaction model and microbial experimental ecosystems for understanding hierarchical dynamics of ecosystems

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ABSTRACT

Understanding ecosystem dynamics is crucial as contemporary human societies face ecosystem degradation. One of the challenges that needs to be recognized is the complex hierarchical dynamics. Conventional dynamic models in ecology often represent only the population level and have yet to include the dynamics of the sub-organism level, which makes an ecosystem a complex adaptive system that shows characteristic behaviors such as resilience and regime shifts. The neglect of the sub-organism level in the conventional dynamic models would be because integrating multiple hierarchical levels makes the models unnecessarily complex unless supporting experimental data are present. Now that large amounts of molecular and ecological data are increasingly accessible in microbial experimental ecosystems, it is worthwhile to tackle the questions of their complex hierarchical dynamics. Here, we propose an approach that combines microbial experimental ecosystems and a hierarchical dynamic model named population–reaction model. We present a simple microbial experimental ecosystem as an example and show how the system can be analyzed by a population–reaction model. We also show that population–reaction models can be applied to various ecological concepts, such as predator–prey interactions, climate change, evolution, and stability of diversity. Our approach will reveal a path to the general understanding of various ecosystems and organisms.

1. Introduction

Understanding ecosystem dynamics is crucial in view of the recent degradation of ecosystem services, which support human life (World Resources Institute, 2005); however, we have yet to understand the features of ecosystem dynamics, *i.e.*, how ecosystems have been organized, sustained, and degraded. It is even difficult to explain the dynamics of simplified experimental ecosystems (Fussmann et al., 2005; Hosoda et al., 2011; Kasada et al., 2014; Tsuchiya et al., 1972). One of the most critical gaps in our understanding is how organisms change their phenotype within the ecosystems, such as by evolution or phenotypic plasticity (Ellner, 2013; Shimada et al., 2010). A phenotype can be considered as an interface between two hierarchical levels in ecosystems: the ecological level, composed of various organisms and environmental factors, and the sub-organism level, composed of tissues, cells, and molecules (Fig. 1A; Holling, 2001; Odum and Barrett, 2005). The sub-organism level changes depending on the status of the ecological level, which, in turn, as the phenotype changes, it affects the changes at the ecological level. Thus, a phenotypic change can determine whether an environmental change is absorbed or amplified to become a considerable impact to the ecosystem. Therefore, to understand how ecosystems change, it is necessary to consider the phenotypic changes that determine and are determined by the interaction between two hierarchical levels (Conrad, 1996; Conrad and Pattee, 1970). In this perspective, we focus on the hierarchy of ecosystems, a core feature that makes ecosystems complex adaptive systems (Levin, 1998) that bring important features such as resilience and regime shifts.

For understanding the features of ecosystem dynamics and their bases, it is effective to conceptualize real systems using a dynamic model, which is a mathematical model that mechanistically describes how the system changes over time (Ellner and Guckenheimer, 2006). For our purpose, it is necessary to integrate the internal dynamics into the model of ecological dynamics.

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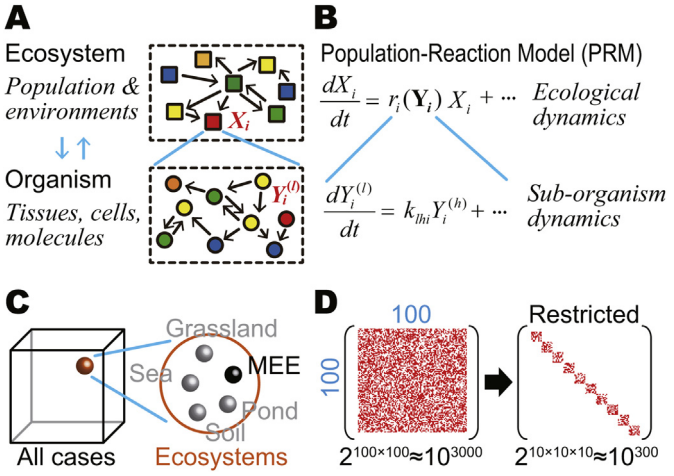

Fig. 1. Ecosystems and population–reaction models. (A) Ecosystem as a hierarchical system. Two hierarchical levels are shown: the ecological level composed of interactions among organisms and environmental components (upper), and the sub-organism level composed of interactions among components inside the organism, such as cells and molecules (lower). (B) Part of the expression of the PRM. X and Y indicate the amount of components at the ecological and sub-organism levels, respectively. X_i is the population of the ith organism in the ecosystem, and $Y_i^{(l)}$ is amount of the lth sub-organism component in the ith organism. A phenotype of the ith organism r_i is expressed by the sub-organism components $\mathbf{Y}_i = \{Y_i^{(1)}, Y_i^{(2)}, \ldots\}$. (C) Schematic presentation of the patterns of the model construction of HNDS. Ecosystems (orange ball) correspond to a tiny fraction among all the mathematically possible cases of HNDS (black cube). Our focus is not on all the cases but the ecosystems (orange ball) including all natural ecosystems and model experimental systems. We consider every MEE (black ball) as one of the ecosystems. (D) Example of a model constraint from hierarchy. Let us consider 10 different organisms, each of which has 10 different sub-organism components, *i.e.*, there are $10 \times 10 = 100$ different sub-organism components in this ecosystem. The logical matrix of the interaction among 100 components is depicted (*i.e.*, a red dot if there is a direct interaction). All the possible cases of the matrix are $2^{100\times100} \approx 10^{3000}$. When we add an assumption stating that there is no direct interaction of sub-organism components among different organisms, all the possible cases can be $2^{10\times10\times10} \approx 10^{300}$, which is one tenth of a whole. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

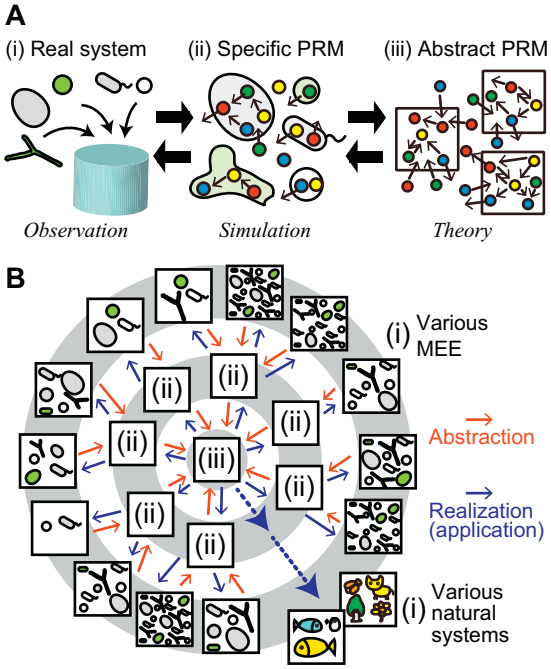

Fig. 2. Proposed approach. The three steps of our strategy. See the text for explanation.

However, this could make the model unfruitfully complex unless supporting empirical or experimental data are available because understanding high-dimensional and nonlinear dynamics is challenging (Blasius et al., 2007; Strogatz, 1994). Currently, the use of microbial systems allows consideration of the molecular basis of the phenotype (Egbert et al., 2010; Karr et al., 2012). Likewise, microbial experimental ecosystems (MEEs) enable us to obtain experimental data from both the ecological and sub-organism levels (Germond et al., 2013; Hosoda et al., 2014; Momeni et al., 2011; Song et al., 2014; Yu et al., 2012). Currently, large amounts of molecular and ecological data are increasingly accessible, and it is worthwhile to consider ecosystems as complex hierarchical systems.

Here, we propose an approach that uses both MEE and a novel framework of dynamic modeling termed as population–reaction model (PRM; Fig. 1B). PRMs are simple fusion of conventional models in population ecology and reaction kinetics, and they consider the amount of components in both ecological and sub-organism levels. Briefly, the phenotype, which has been conventionally expressed as rate constants in the Lotka–Volterra equations, is not a constant but a function of the amount of the sub-organism components in the PRMs. In PRMs, a change at the ecological level affects the changes in the sub-organism level and *vice versa*. PRMs are primitive and intuitive because they are based on a conventional way. In addition, they can be compared with experiments of MEEs directly because they include the amount of components in both levels. Our proposed approach using MEEs and PRMs has 3 steps: (i) a MEE is constructed as a real system, (ii) the dynamics of the MEE is analyzed by a specific PRM, and (iii) an abstract PRM is constructed to highlight the common features of the ecosystem dynamics from the knowledge of various MEEs (Fig. 2, see below). Because the abstract PRM is based on various specific PRMs that correspond to real systems, the consequent theory grasps the real systems with generality. Below, we describe key challenges, our proposed approach, and examples of PRMs.

2. Challenges

Here, we outline the general challenges for understanding complex dynamics using dynamic models. It is challenging to manage high-dimensional ("high" means greater than 5–10; Kaneko and Tsuda, 2003; Smale, 1976) and nonlinear (having nonlinear terms such as predator–prey terms of the Lotka–Volterra equations) dynamic systems (HNDS; Blasius et al., 2007; Strogatz, 1994). Nonlinear systems cannot be understood solely as a sum of simple parts; instead, they requires us to consider the "system as a whole" comprehensively even it is high dimensional in contrast to linear systems where the entire system is the same as the sum of the parts. High dimensionality requires us to consider vast numbers of options in the model construction (known as the curse of dimensionality, *e.g.*, in a dynamic model of 100 component, $2^{100\times100} \approx 10^{3000}$ of possible interaction patterns exist even if we only consider binary pairwise interactions), despite the fact that small differences in the model assumptions could result in partially contradictory conclusions (May, 1972; Mougi and Kondoh, 2012). Hence, we usually try to decrease the dimensions of the dynamic model by considering only a few components of interest, on the assumption that the other components are negligible. This procedure is effective to understand certain aspects of complex HNDS. Indeed, HNDS can partially show ordered (as opposed to chaotic) phases that can be approximately explained by a few effective dimensions; however, various small changes accumulate as history in other unnoticeable dimensions, and HNDS can suddenly change its state to another phase depending on its history (Kaneko and Tsuda, 2003). Such sudden changes depending on its history can be interpreted as remarkable events in ecosystems such

as a regime shift (Scheffer and Carpenter, 2003). Therefore, we must consider HNDS to understand phase changes of ecosystem, *i.e.*, the ecosystem dynamics, despite the above challenges.

We need to restrict options for model construction in HNDS by evidential constraints. Likewise, we need to focus on features specific to ecosystems, not only common features in all the mathematically possible HNDS. The dynamic models that map ecosystems must be only a small fraction among all the possible patterns in the model construction (Fig. 1C). Hierarchy plays a role as the constraints of the model construction when we consider sub-organism components in ecosystems. For example, if we assume that sub-organism components of an organism do not have a direct interaction with those of other organisms, the number of possible patterns of interactions dramatically decreases (nested structure; Fig. 1D). The model can lose the ability to consider the direct interaction of sub-organism components between different organisms by this model constraint from the hierarchy; however, indirect interactions *via* environment, bringing interaction between two hierarchical levels, can be considered. Additionally, we can add an exception to the constraint, *e.g.*, the sub-organism components of an organism can be directly transferred into another organism by predation. Likewise, a dynamic model with this constraint from hierarchy (thus, including PRM) does not answer how the given hierarchy emerges, *e.g.*, how organisms emerge from molecules through self-organization; instead, it answers how the system changes over time if hierarchy is present.

The constraints and exceptions in the model construction should be consistent with the real world. We already know various constraints from natural observation, *e.g.*, structures of the food webs (Dunne et al., 2002; Guimera et al., 2010), and from biological knowledge, *e.g.*, structures of gene regulatory networks and metabolic networks (Barabasi and Oltvai, 2004). Recently, several studies have used dynamic models that integrate genome-scale metabolic stoichiometry from databases for both natural (Larsen et al., 2011, 2015) and experimental (Harcombe et al., 2014; Wintermute and Silver, 2010) microbial ecosystems. However, those models do not simultaneously consider the amount of components in both levels and they lack histories stocked in the internal states, which are important as stated above. Then, we must consider more complex models and determine which constraint is necessary to understand the feature of the real ecosystem dynamics. A simpler model is better for our understanding as long as it can explain the observed phenomena. Therefore, it is necessary to compare a dynamic model with real phenomena in a systematic fashion for both hierarchical levels. Thus, we need PRMs and MEEs with comprehensive analyses.

3. Proposed approach

We propose to constrain the options for model construction of PRMs in the light of data derived from MEEs. This proposition calls for the 3 steps that involve (i) real systems (*i.e.*, MEEs), (ii) specific PRMs, and (iii) abstract PRMs (Fig. 2A). Below, we explain the fundamental roles played by MEEs, and then illustrate how MEEs can inform on specifying and abstracting PRMs (see next section for a simple example). We emphasize that the abstraction is used both solely for decreasing the number of considered components (*i.e.*, dimensions; Schaffer, 1981) and for obtaining simple rules for the model construction even if a large number of components remain to be considered.

(i) Each MEE plays a role not only as a proof tool of a known principle but also as a real system that highlights novel unknown features. This constructive and phenomenological approach using real experiments follows the same approach using *in silico* experiments that were performed for a long time (Conrad and Pattee, 1970). In this approach, we construct a complex system of which we know all the components but we do not know its dynamic behavior. We observe phenomena in this "defined" complex system to connect its behaviors with the known properties of the system, and, then, we understand the features of the system by analyzing the mechanism of the phenomena. For the real system to be analyzed, MEEs have great advantages because we can directly model the dynamics of interacting entities both at the population and the sub-organism levels, thanks to the accumulated knowledge about microbiology and the technical advances in molecular biology (Benton et al., 2007; Hindre et al., 2012; Jessup et al., 2004). MEEs enable us to mix the organisms in an arbitrary combination without unknown organisms, to stock the organisms at an arbitrary time, to observe reproducibility and contingency, and to observe even system's breakdowns and failed establishments. Technically, population-level variables can be measured using microscopy, spectroscopy, cytometry, and metagenome analysis; the state of organisms, such as internal molecules or genetic information, can be estimated by metabolome, transcriptome, proteome, and genome analyses. Those high-throughput data are subject to statistical analyses for both visualizing phenomena and inspiring hypotheses for specific PRMs (ii). Thus, MEEs enable us to systematically and reproducibly analyze the ecosystem dynamics at/across different levels. Because our immediate goal is to uncover the common features that could underlie the dynamics of all ecosystems, we emphasize that various MEEs should be investigated, *e.g.*, synthetic (De Roy et al., 2014) and field-based MEEs (Foster and Bell, 2012; Kato et al., 2014), as well as from single (Barrick and Lenski, 2013) and diverse population MEEs (Hairston et al., 1968).

(ii) A specific PRM for each MEE is tailored to its experimental setup and results, where a given collection of variables are considered both at sub-organism and population levels. The PRM considers the amount of both population and sub-organism components. Phenotypes are not constant but functions of the sub-organism components, which can be subject to chemical reactions. The resolution of internal reactions depends on the requirements for explaining the MEE, *e.g.*, a biosynthesis of alanine from glucose can be expressed as a single reaction with a constant rate, as a single reaction in which its rate depends on the amount of glucose and corresponding enzymes that are also variable, or as multi-step reactions depending on various sub-organism components. The PRM model-fitting is built upon an iterative and adaptive process of fitting the outcomes of simulation to the experimental results, either through performing another experiment or through revising the model formula of the PRM. The initial version of the dynamic model should assume a constant phenotype (*i.e.*, not the PRM but a population model without sub-organism level) because the model should be as simple as possible as long as it can explain the population dynamics; however, it is likely to be necessary to include the phenotypic changes in most cases of MEE, unless the cultivation is very short without any environmental change. Then, we need a hypothetical mechanism based on the sub-organism level to construct the specific PRM. The analysis of a MEE with a specific PRM based on the hypotheses gives us a simple interpretation (abstraction) of each of the real MEEs, and a set of the dynamical parameters from various systems can be used to develop the abstract PRM for the next step.

(iii) The abstract PRM is a toy model constructed by a set of simple rules and does not assume any specific components, which explain various phenomena by a simple mechanism. Hence, the abstraction should be conducted using knowledge based

on various real systems. Therefore, the obtained theory with the abstract PRM can help us highlight the common features of ecosystems to summarize the dynamics of various real ecosystems and to also construct specific PRMs for explaining or forecasting novel systems (Fig. 2B). Even if the system is HNDS, simple rules for the model construction that provides appropriate constraints enables us to focus on the ecosystem dynamics, evading the curse of dimensionality. This ultimate abstraction requires direct or indirect (*e.g.*, *via* studies) collaboration between experimental, field, and theoretical researchers in various disciplines.

4. A simple example of a population–reaction model with experimental data

Here, we show a simple example of a real system and a corresponding specific PRM to reveal how phenotypic changes by plasticity can be integrated in ecological dynamics (Fig. 3A). We also discuss how this strategy can contribute to a general understanding that can be applied to other ecosystems.

We present a simple case of a MEE that consists of two *Escherichia coli* populations. Two different genetically engineered populations of *E. coli* were previously mixed to construct a synthetic syntrophy to investigate how two organisms that have not previously been in contact can establish a mutualism (Fig. 3A (i); (Hosoda et al., 2011). Two populations, I^- and L^-, were isoleucine (Ile) and leucine (Leu) auxotrophs, respectively, and each lacked one of the genes necessary for the biosynthesis from nutrients in the medium (mainly glucose (Glc)). Neither population achieves population growth unless the required nutrients are externally supplemented or they compensate a sufficient amount of the required nutrients for each other in co-culture. In the previous study, the population and environmental components were measured by flow cytometry and a bioassay, respectively (Fig. 3A (ii), upper), and the phenotypes (growth and nutrient supply) of I^- and L^- were determined. The analyses revealed that L^- cooperatively increased Ile-supply more than ten-fold when the two were mixed and before its own population grew, which suggested the increased concentration of Ile in L^- (Ile_2, supposedly plotted in Fig. 3A (ii), center, on the assumption that the supply correlates to the internal Ile concentration). A transcriptome analysis revealed the changes in the internal state of L^- accompanied by the increased Ile-supply; however, the analysis did not show any significant increase in the expression of genes related to the Ile biosynthesis (Fig. 3A (ii), bottom). Thus, L^- changed its phenotype in response to the first encounter, which contributed to the establishment of the syntrophy, but the basis of the phenotypic plasticity was still unclear.

Here, we explain the observed phenomena by a specific PRM (Fig. 3A (i)). Simply following the setup, the model includes the two populations (I^- and L^-), the amount of environmental components (Glc_0, Ile_0, Leu_0), and the concentration of internal molecules in each organism (Glc_i, Ile_i, Leu_i; $i = 1$ or 2). Chemical reactions occur inside the organisms (black arrows in Fig. 3A(i), *e.g.*, Glc_2 to Ile_2), and ecological events occur as a result of the chemical reactions: population growth occurs as a reaction using the three molecules (Ile, Glc, and Leu), and the nutrient supply and uptake occur depending on the concentration of nutrients inside and outside the organisms (Supplementary text). Based on this model, in the co-culture where

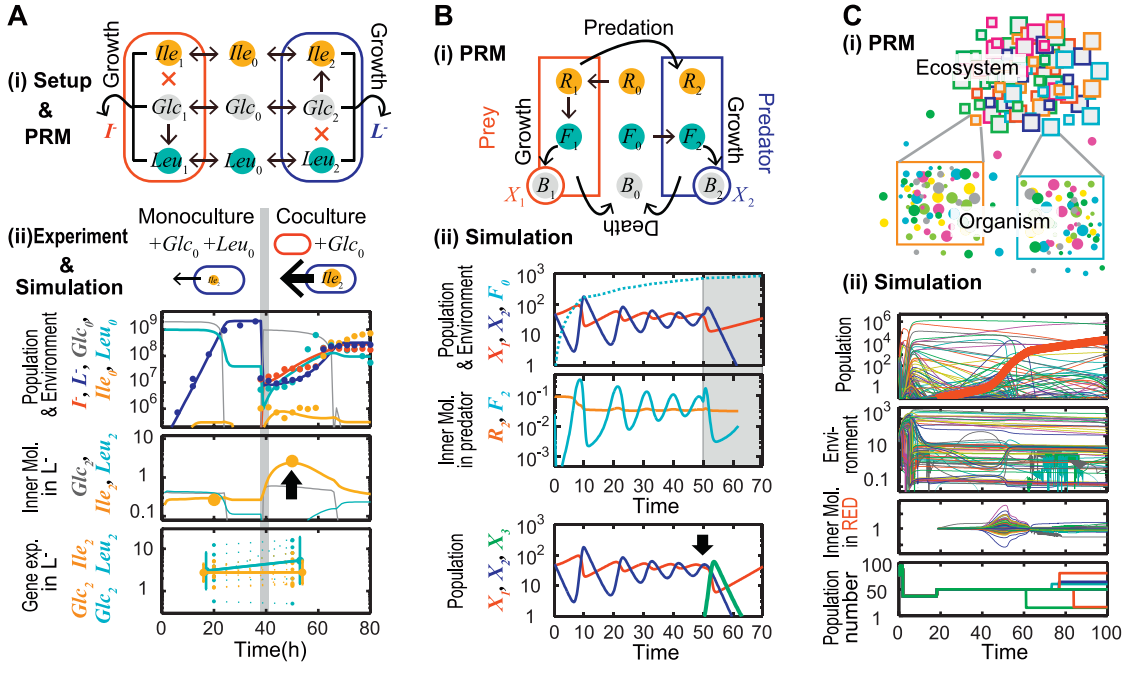

Fig. 3. Examples of PRMs. (A) Specific PRM for a synthetic syntrophy of two populations of *E. coli*. In the scheme (i), black arrows indicate the reactions, and red crosses indicate the reaction where the corresponding gene is lacking. Experimental results from the previous work (partially supposed) and simulation results are shown in (ii) as dots and lines, respectively: the population (cells/mL) and the amount of environmental molecules (cell equivalent amount/mL; upper), the concentration of internal molecules in L^- (a.u.; middle), and the gene expressions that correspond to the reaction rate of Glc to Ile and Glc to Leu (a.u.; lower; dotted lines indicate all the genes that belong to the category of the Ile or Leu biosynthesis; the bold line indicates the geometrical average and the standard deviation, which do not show significant change). The colors of plots correspond to the colors of the letters shown in the vertical axis. In the simulation, the culture condition is changed at time 40 h (gray line) from monoculture of L^- externally supplemented by Leu to a co-culture with I^- in the absence of external supplement of Leu. Note that the supposed experimental data are shown for the explanation and are not completely accurate; the co-culture was actually conducted from the late growth phase of the monoculture in the experiments, and the Ile_2 is supposedly plotted from the fact that L^- increased the Ile-supply more than ten-fold in the co-culture. (B) A predator–prey PRM. Formats are the same as (A); see text for the explanation. (C) PRM for a diverse ecosystem composed of 100 populations, each of which contain 100 types of sub-organism components and 100 types of environmental components (i). The simulation results over time (ii) are shown in the following order from the top: population, amount of environmental components, concentration of sub-organism components of an organism whose population is depicted as bold red, and the genetic lineage of the novel populations that emerge from mutation in the bold red population. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Glc is supplemented externally, I^- and L^- uptake Glc and synthesize Leu and Ile, respectively. Then, I^- and L^- supply Leu and Ile to the environment, and uptake the Ile and Leu, respectively. Both I^- and L^- grow according to the reaction using the three molecules (Ile, Glc, and Leu). Fig. 3A (ii) shows the simulation results overlaid by the experimental results. The PRM can explain the phenotypic plasticity (increase in Ile_2; center) even under the restriction that all of the kinetic constants are the same between I^- and L^-, except the reactions where they lack a gene. The basis is simply that Ile_2 accumulates in the co-culture because the cells cannot use Ile_2 for growth due to the lack of Leu_2, although this hypothetical mechanism has not yet been proven. Note that the aim is not to find the best fit model but to abstract real systems for our understanding.

What does this approach provide us? First, it reveals what we should investigate next. In this case, for example, the task ahead is to measure the internal metabolites, for instance, by metabolome analysis. Second, it may increase our general understanding. In the hypothetical mechanism, the phenotypic change was simply due to the clogging in the material flux, which is a natural outcome without sophisticated functions of organisms. This result suggests that this type of phenotypic change is not specific to this case but can be generalized by an abstract PRM. This outcome may open up a path to novel theories that can be applied to other ecosystems. It should be emphasized that the result (or consequence) of the MEE was rather surprising and led us to arrive at the idea phenomenologically. Thus, there exists a fundamental gap between current knowledge and observed phenomena. It is suggested that any MEE has the potential to yield important findings if we comprehensively observe the ecosystem dynamics in various conditions.

5. Further examples: predator–prey interactions, climate change, evolution, and diversity

Here, we show further examples considering other important ecological concepts such as predator–prey interaction, climate change, evolution, and stability of biodiversity. The first example is about the formulation of predation using a simple PRM of a predator–prey system (Fig. 3B (i); simplified for explanation, regardless of reality). Predation is a basic interaction among organisms in a food web, which is hierarchically different from internal chemical reactions. The prey (X_1) takes a resource molecule (R) from the environment and synthesizes the functional molecule (F), which changes itself to the body material (B) as the population growth. The predator (X_2) takes the prey into its own body, which is formulated as the transfer of the prey's internal molecules (R_1, F_1, B_1) to the predator's internal molecules (R_2, F_2, B_2) along with a decrease in the prey's population (Supplementary text). Note that predation does not directly increase the predator's population, as in the Lotka–Volterra model, but rather increases the amount of internal molecules, which leads to the growth reaction. When organisms die spontaneously (not by predation), all their internal molecules are released into the environment. Both phenotypes, growth and predation, depend on internal molecules F. Fig. 3B (ii) shows the simulated population dynamics and the internal reaction kinetics of the predator (upper and center, respectively; time until 50). We can see that F and, thus, phenotype of the predator varies in the oscillation dynamics.

We next consider climate change and evolution by using the same predator–prey PRM and discuss why such events should be considered with a PRM. As an example of the effect of a climate change, we change the rate constants of all the internal reactions to be 70% of the original in the gray area of Fig. 3B (ii; upper and center; time after 50), which roughly simulates the effect of temperature changes. We can see that this 30% change of internal reaction leads to the breakdown of this stable-looking predator–prey system, like temperature chaos (Jonsson et al., 2002). As an example of the effect of evolution, Fig. 3B (ii; bottom) shows the simulated effect of the emergence of a new predator population by mutation (at time 50). The only difference in the new predator (X_3, green) is that its rate of growth reaction is reduced by half, which leads to a higher internal F concentration followed by a higher predation rate; this chain of events results in a higher growth rate of the new predator and population takeover from the original predator (X_2, blue). As a result, we can see the breakdown due to a small change in a single internal reaction by evolution even without any external perturbations. What is then the advantage in considering such concepts in a PRM? Both the response to temperature change and the evolutionary change depend on the construction of organisms, such as physical structure or networks of internal reactions. The construction is strongly restricted by both the ecological level, such as natural selection, and the sub-organism level, such as physical constraints. Indeed, organisms can change in a limited fashion in various levels of evolution (Krishna and Grishin, 2004; Morris, 2010; Suzuki et al., 2014; Tenaillon et al., 2012; Travisano et al., 1995); *i.e.*, organisms are not "almighty". Even the mutation rate, *i.e.*, a rule of change itself, could change in a trend (Kaneko and Ikegami, 1992; Wielgoss et al., 2013). This outcome suggests the existence of a general rule and the potential of predictability, to a certain extent, which should be understood by considering the internal structure using PRMs.

The above two examples represent extraordinary simple ecosystems. It is necessary to investigate MEEs that have larger biodiversity. MEEs of more than 10 species have already been investigated (Hairston et al., 1968; McGradySteed et al., 1997); however, their internal dynamics have yet to be integrated. Fig. 3C (i) shows an example of a PRM of 100 populations, each of which comprises 100 types of internal molecules. This PRM includes changes in the populations (Fig. 3C (ii), top) and in the environmental components (second), as well as phenotypic plasticity (third) and evolution (bottom). MEEs can provide us the corresponding data about such parameters. The analysis of MEEs with large biodiversity would enable us to understand the stability of biodiversity, *i.e.*, how biodiversity is organized, sustained, and lost.

6. Conclusion

We presented a strategy for understanding ecosystem dynamics with phenotypic change using MEEs and PRMs. In this perspective, our examples focus on simplicity for explanation; however, it is necessary to consider more complex systems in PRMs with other concepts such as contingency (Hekstra and Leibler, 2012), materials cycling (Degermendzhi et al., 2009; Vanvoris et al., 1980), and spatial structure (Harcombe et al., 2014). It is easy to add other concepts such as spatial structure in a conventional way in either field of population ecology or reaction kinetics because the PRM is a fusion of conventional models in those fields. It would also be necessary to consider upscaling from small-scale experiments to the prediction of large-scale patterns (Denny and Benedetti-Cecchi, 2012; Melbourne and Chesson, 2005). The obtained understanding of ecosystems will also result in an improved understanding of the organisms themselves with new insights into phenotype, fitness, and the niche in high-dimensional ecosystems (Clark et al., 2007). Moreover, this understanding would lead to important applications such as ecosystem conservation by utilizing inherent dynamics of the systems (Cornelius et al., 2013; Liu et al., 2011) and bioprocessing by a multi-population MEE, which is essentially analogous to controlling ecosystem services (Mee and Wang, 2012; Pandhal and Noirel, 2014; Shong et al., 2012). We also speculate that it may lead to a general understanding of the physical basis of all the other biological systems as hierarchical HNDS, followed by a wide range of biological applications, such as medical or biologically

harmonized technologies (*e.g.*, molecular communication; Nakano, 2013; or machine learning for biological dynamics).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biosystems.2015.12.005.

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