DEB Modeling for Nanotoxicology, Microbial Ecology, and Environmental Engineering:
Comment on “Physics of metabolic organization” by Marko Jusup et al.

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Jusup et al. [1] appeal to mathematical physicists, and to biologists, by providing the theoretical basis for dynamic energy budget (DEB) modeling of individual organisms and populations, while emphasizing model simplicity, universality, and applicability to real world problems. Comments herein regard the disciplinary tensions proposed by the authors and suggest that—in addition to important applications in eco- and specifically nano-toxicology—there are opportunities for DEB frameworks to inform relative complexity in microbial ecological process modeling. This commentary also suggests another audience for bridging DEB theory and application—engineers solving environmental problems.

1. Nanotoxicology as an exemplar domain application for DEB modeling

Although few synthetic chemicals in commercial use have been examined for their toxicity to humans or to environmental receptors [2], the rapid advent of new classes of materials manufactured at the nanoscale (with 1 or more dimensions <100 nm) punctuates the opportunity—and need—to assess new chemical hazards alongside commercial

proliferation and expected exposures. Hazard assessment applied to manufactured nanomaterials (MNM), referred to as “nanotoxicology”, can inform the safe development of nanotechnology through discovering mechanisms of MNM biological toxicity [3, 4]. Because many MNMs are already in high production [5] and incorporated into consumer goods with eventual environmental disposal, some efforts regard how MNMs could affect ecological receptors in ecosystems [6]. Among the possible ecological receptors, microorganisms—primarily bacteria—are likely exposed to MNMs and other micropollutants since bacteria are abundant and environmentally ubiquitous [7].

The societally-relevant reasons to study bacteria as probable MNM receptors [8] include bacterial centrality to the valuable ecosystem services [9] of nutrient cycling, and of waste treatment including pollutant biodegradation [8]. Some bacterial taxa that are opportunistic pathogens are also versatile pollutant degraders and resistant to toxins including heavy metals. Such is the case for an environmental strain of *Pseudomonas aeruginosa*, a model organism used for researching whether CdSe quantum dots (QDs), i.e. semiconductor nanocrystals for many uses from cell labeling to photovoltaics to digital displays, were differently toxic relative to the constituents cadmium and selenide [10]. As described by Jusup et al., Section 8.5.3 [1], a first DEB model that focused on planktonic *P. aeruginosa* population growth in response to varying cadmium concentrations [10] successfully predicted bacterial growth curves for “untested” Cd concentrations, i.e. beyond data used for DEB model parameter estimation [11]. This DEB model [11] was thus capable of predicting bacterial population growth as a function of Cd concentration. As such, the model expands the reach of the original experimental work and thus of potential ecological risk assessment. This DEB model [11] invokes established effects mechanisms (e.g. the

energetic cost of driving transmembrane Cd efflux pumps, and the accumulation of intracellular reactive oxygen species or ROS that lead to the formation of damage inducing compounds), and allows for testing hypotheses regarding measured (in this case, ROS at one time point) and unmeasured (e.g. efflux pump activity) toxicity manifestations [11]. However, the DEB model transcends predicting population growth curves: it also reveals the timing and nature of organismal coping processes that are occurring during toxin exposure (e.g. cellular adjustment during the population lag phase) [11]. As such, this DEB model [11] is a window into the inner workings of the toxicity experience for the bacterial population. Such understanding tethers to, but richly transcends, simple experimentally-derived first order specific growth rates (μ , t^{-1}) whose measurement, as endpoints for Monod kinetic modeling, cannot explain the observed toxicity beyond dose-dependencies. While biologists and chemists conceived of and performed the original experiments [10], DEB modelers developed a deep mechanistically-based interpretation of the population dynamics that also afforded growth curve prediction [11].

In studies of potential CdSe QD effects to *P. aeruginosa* [10], cadmium salts were positive controls for testing nanoparticle-specific effects relative to the constituent metal [12]. Experimentally determining a nanoparticle-specific effect was by deduction: dissolved Cd concentrations could not fully explain reductions in μ from CdSe QD exposures [10]. As per Jusup et al., Section 8.5.3 [1], the DEB model [13] allowed for more thorough hypothesis testing of population growth effects: to what extent did effects originate from total administered cadmium, versus either dissolved cadmium or a combination of dissolved cadmium and residual CdSe QDs? Beyond mathematically proving that growth effects owed to nano-specific QD toxicity, the model narrowed the mechanistic

explanations of toxicity to cellular acclimation and increased maintenance during growth [13]. While the laboratory experiments alone suggested a CdSe QD nanoparticle-specific effect to a growing *P. aeruginosa* population [10], the DEB model ruled out other causes for growth curve variations plus provided mechanistically-based explanations for dose-dependent growth impairment anchored in maintenance investment for repairing cellular damage [13].

The applications of DEB modeling in predictive nanotoxicology and for nanotoxicity mechanism discovery are delineated in a more thorough examination of ecological nanotoxicology [6], and reinforced in a critical review regarding paths forward in assessing environmental implications of MNMs [12]. To the experimental nanotoxicologist faced with prioritizing test efforts for myriad possible MNMs, exposure conditions, and biological receptors [12], the value of DEB modeling to guide and interpret experimentation is vast. More broadly, mechanistically-based MNM hazard predictions stemming from DEB models of biological processes, coupled to MNM exposure models for ecologically-relevant receptors, are promising long term vehicles for meaningful MNM environmental risk assessment [12].

2. Microbial ecology and environmental engineering concerns

From microbial ecology and environmental engineering perspectives, the “simplicity” as per Jusup et al. [1] (Section 2) of DEB representations of higher organisms has substantial embedded complexity. This observation owes to the representation of digestion that occurs between macroorganismal ingestion and egestion in Jusup et al. (Table 2 and Section 4.1)[1], juxtaposed against the growing recognition that complex

bacterial communities underpin digestive (and other) systems in animal hosts [14]. Recent syntheses do not clarify the importance of bacterial community structure to ecosystem function [15], yet soil microbial communities may currently be responding to climate warming by accelerating soil carbon decomposition—which constitutes a worrisome positive feedback [16]. As Jusup et al. [1] (multiple locations, throughout) feature “climate change” as a motivator for DEB modeling, and as complex microbial communities can apparently be embedded rather simplistically in modeling frameworks, perhaps DEB models could assist predicting soil responses to climate warming towards potential management action.

A last observation regards environmental engineering, an inherently systems-oriented field where training is steeped in mass balance- and energy balance-based models of biological processes subject to physicochemical phenomena and environmental factors. There are two main observations. First, recognizing the disciplinary tensions (physical mathematics to biology) addressed by Jusup et al. [1], environmental engineering would seem to straddle these domains and could serve as a disciplinary ambassador for DEB modeling. There could be great interest in DEB modeling by environmental engineers, since Monod kinetics features in reaction modeling, e.g. of biodegradation. Predicting kinetic coefficients via DEB modeling could build from published coefficients and thereby expand biodegradation modeling opportunities to unstudied concentration or condition regimes. Second, the emphasis in DEB models on “aerobic heterotrophs” as per Jusup et al. [1] (Section 2) might expand, e.g. to organisms using exotic terminal electron acceptors such as either chlorinated solvents or metals. Processes such as reductive dechlorination or metal respiration, similarly to atmospheric N_2 fixation carried out by sensitive plant-bacterial

symbioses [17, 18] constitute rare functions encoded by uncommon genetic elements that are less likely to be represented by DEB models described by Jusup et al. [1] (Section 2, “Cell similarity”). Yet rare microbial processes may be highly vulnerable in an increasingly warm and polluted world, and thus could be worthy future emphases for powerful DEB modeling approaches that would appeal to microbial ecology and environmental engineering concerns.

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