VNIVERSITAT DE VALÈNCIA Institut Cavanilles de Biodiversitat i Biologia Evolutiva

Valencia, September 22th, 2016

Dear Dr. Gilbert,

Please find uploaded the manuscript entitled "Health and disease imprinted in the time variability of the human microbiome" by Jose Manuel Marti *et al*., for your kind consideration for publication as a Research Article in *mSystems.*

There is general assent on the need for methodologies that can help to unravel the increasing amount of –omic information being generated on microbial diversity. In this paper we examine the dynamic association between gut microbiota and human health. Our work shows how a universal fluctuation scaling law, which describes the temporal variability of the system, can help us to distinguish healthy from sick microbiota. It is also revealed a mechanistic explanation, based on the statistical theory of errors, which predicts two distinguishable phases of the gut microbiome. We have applied this framework to data generated in our lab from IBS patients, and then extended this procedure to other publicly available data of other studies which have microbiota perturbations of different nature. Data analyzed in this project indicates that a noise induced phase transition corresponds to the route leading to disease. The universal law and the mechanistic model proposed in this paper can be applied to virtually any temporal (or spatial) set of high throughput genetic data in environmental and animal microbial metagenomes.

We hope you will find our work as promising as we think and consider it suitable for publication in *mSystems*.

On behalf of all authors, sincerely

Jose Manuel Martí and Daniel Martínez-Martínez