Simulating the Influence of Diet on the Intestinal Microbiome Composition

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Diet is a driving factor in the emergence of western lifestyle disease, and of the gut microbe community (microbiota) composition, which in turn has been linked to a host of diseases. There are many dimensions comprising 'diet': *macro-nutrient distribution*, the proportion of protein, carbohydrate and fat in food; *energy density*, the ratio of calories to food weight; *intake pattern*, the times at which we eat, and our incorporation of periods of fasting; and *macronutrient source*, such as carbohydrates in the form of sugar, complex carbohydrates or fibre. The rational design of diet interventions requires the integration of all these dimensions, which is challenging to do experimentally.

We are developing a simulation that integrates these diet dimensions to investigate how diet drives microbiota community composition. The simulation is agent-based, and explicitly represents individual bacteria cells and their location in the gut. We assume bacteria require access to carbon (C) and nitrogen (N) in a ratio of 5.2:1, and one of these is always a limiting factor on growth; we assume all other nutrients are freely available. Bacteria internalise C and N from their specific substrates in the local environment. Internalised stores of C and N decay, representing the 'cost of living', and their absolute quantity determines a bacterium's probability of division or death. The gut is represented as a 1-dimensional space, with bacteria and digesta progressed through peristalsis events. The microbiota community composition is defined in terms of six 'functional guilds', based on bacteria substrates, which may be diet-derived macronutrients or mucin glycoprotein host-secretions. Long-chain and shorter-chain carbohydrates are represented, as is casein; these are components of real diet formulations input to the simulation. Protein contains both N and C, whereas carbohydrates provide only C. The mucin secretion rate has been estimated based on empirical data. Guild members compete for substrates, but do not otherwise interact.

A real-world data set of 30 diets, comprising 10 macronutrient distributions and 3 energy densities, administered to 250 cages of mice is used to parameterize the simulation [2]. The averaged food consumption of each cage is known, and used to plot that cage's location on a macronutrient landscape. Interpolation between the 250 simulated cage datapoints reveals how different diets promote or disadvantage particular guilds. For example, figure 1 shows the relative abundance (% of total bacteria) of an example guild across the space of diets comprising different ratios of carbohydrate to protein. This particular guild ferments wheat starch and diet-derived protein. It is most competitive on diets comprising roughly equal quantities of each. Attributing real bacteria to guilds is problematic, as many are functionally diverse and satisfy the conditions of several guilds. Nonetheless, the caecal contents of real mice across this diet landscape have been sequenced, and the resultant landscapes of bacteria that can be assigned a guild, such as *Akkermansia muciniphila*, match those of their corresponding simulated guild.

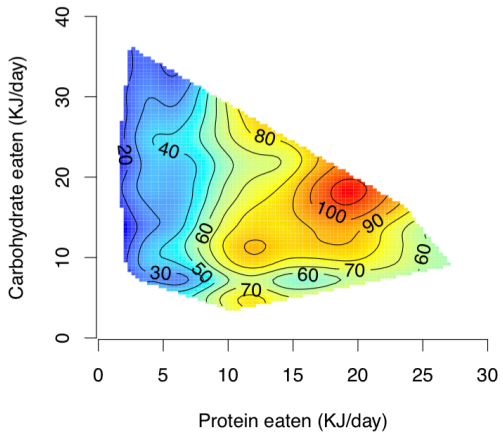

Figure 1: Relative abundance (%) of guild growing only on diet-derived protein and long-chain wheat starch carbohydrates across the diet landscape.

We have thus far examined how periodic fasting and the administration prebiotic fibres, both individually and in concert, shape the microbiota.

References

[1] Solon-Biet, S., *et al.* (2014). Cell Metabolism, 18:418-420.