HEALTHY BIRTH, GROWTH & DEVELOPMENT

Quantitative Physiologic Model of the Interaction Between Nutrition and Infection to Determine the Energy Available for Growth

Michael Morimoto,[1] Lyn Powell,[1] Rajalakshmi Santhakumar,[2] Aaron Gowins,[3] Joanne Arsenault,[4] Carson Chow,[3] Rukmini Kumar,[2] Quantitative Physiologic Modeling team,[5] Representing the Healthy Birth, Growth, and Development knowledge integration (HBGD*ki*) Community[5]

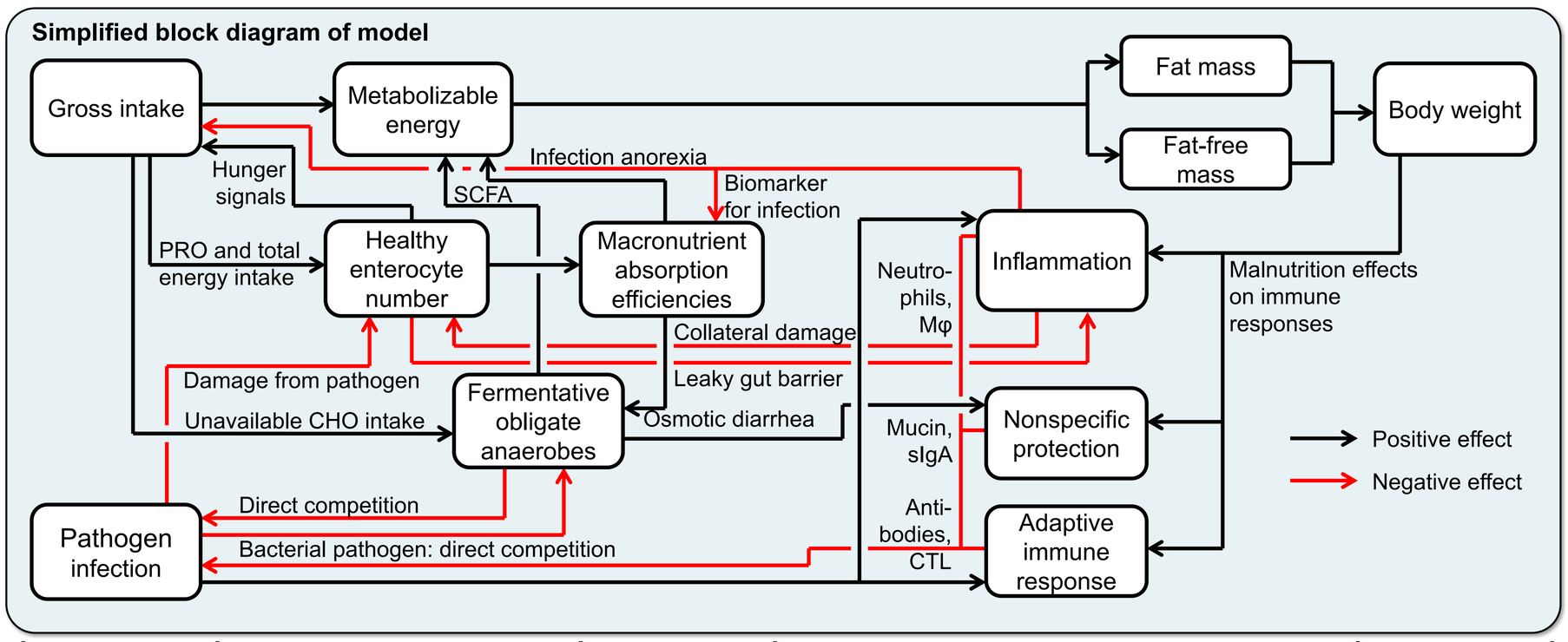
[1]Lynx BioConsulting, USA; [2]Vantage Research, Chennai, India; [3]National Institutes of Health, Bethesda, MD, USA; [4]University of California Davis, Davis, CA, USA; [5]Bill & Melinda Gates Foundation, Seattle, WA, USA

Objectives

- **To develop a quantitative physiologic model that represents the major causal dependencies relating nutritional status and enteric pathogen exposure to macronutrient and energy availability.**
- **To apply the model to better understand and predict effective interventions for growth faltering in children in low- and middle-income countries.**

Overview of model scope, calibration, and validation

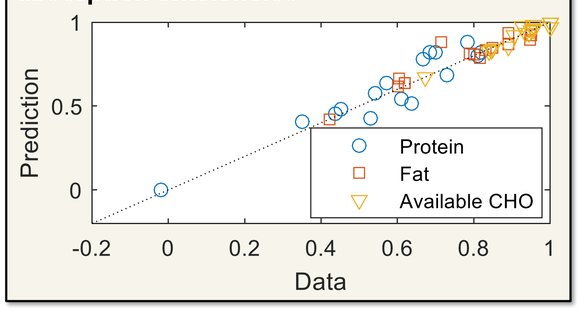
Simplified block diagram of model



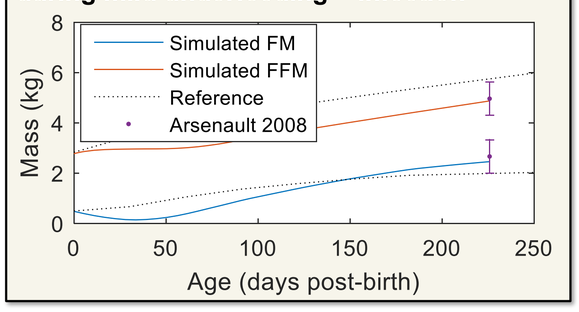
Calibration example: virus recovery times

	Well-nourished data	Simulation
Shedding	8 – 10 days	9.24 days
Inflammation	NA	24.10 days
Barrier function	8 – 18 days	15.89 days
Absorption	NA	25.70 days

Calibration example: metabolizable absorption efficiencies

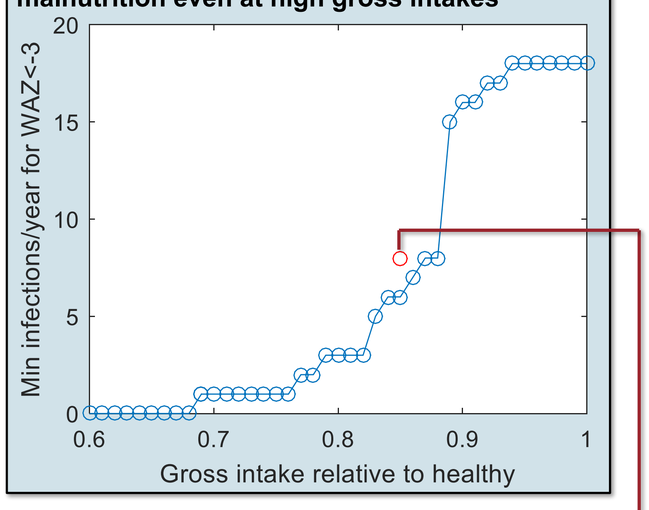


Validation example: body composition during mild underfeeding + infection

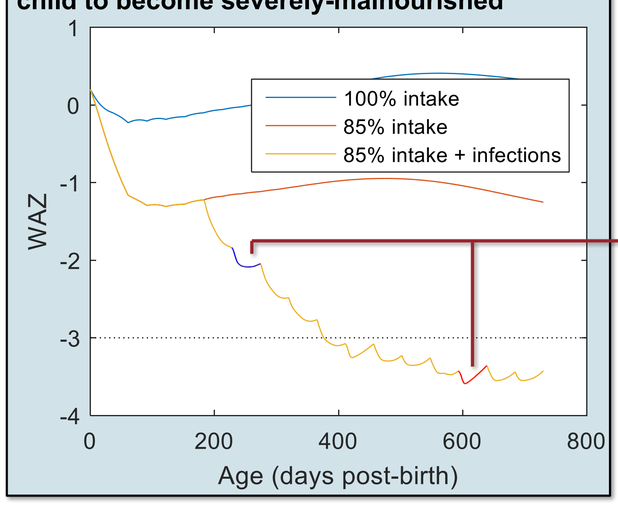


Simulation results illustrating the role of infections in growth faltering

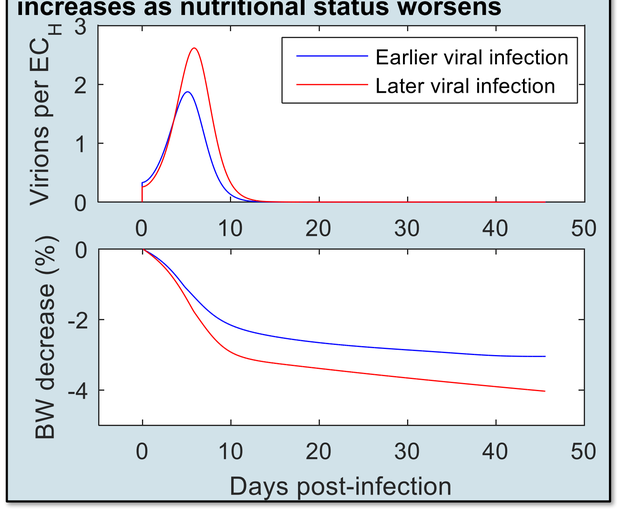
Repeat infections may result in severe malnutrition even at high gross intakes



Infections may cause a mildly-malnourished child to become severely-malnourished



Synergistic interactions: infection severity increases as nutritional status worsens



Methods

- A detailed review of published literature was performed.
- A 23-state nonlinear differential equation model was developed.
- The model represented major causal mechanisms connecting nutrition and pathogen exposure to macronutrient and energy available for metabolism and growth.
- The model focused on the gastrointestinal (GI) tract due to its role in relating gross nutrient intake and enteric pathogen infection to nutrient absorption.
- The model included dynamic representations of bacterial and viral pathogens, microbiota constituents, and innate and adaptive immune responses that affect nutrient absorption by changing the number of healthy enterocytes and increasing protein mucosal demands during malnutrition and infection.
- Published quantitative data and qualitative expectations were used for calibration, validation, refinement of the functional forms of the differential equations, and enforcement of local behavior around phenotypes (such as parameter values to guarantee stability of healthy equilibria).

Results

- A wide range of biological domains and data sources were combined in the model.
- The model exhibited larger-scale behaviors that resulted from mechanistic interactions of the smaller subsystems.
- The model confirmed the prevailing hypothesis about the cause of environmental enteropathy and illustrated the "synergy"/super-additivity between the effects of undernourishment and infection on growth faltering[1,2]:

(1) Malnourishment increases susceptibility to infection.

(2) Recovery time and severity of GI damage after acute infection increase during malnutrition.

(3) The increased duration and severity of GI damage cause prolonged duration and magnitude of malabsorption and further deterioration of nutritional status.

- The model predicted that repeated exposure to enteric pathogens may create a cumulative energy deficit that is large enough to cause a child to fall off a normal growth trajectory, despite age-appropriate required gross intake.

Conclusions

- **Model simulations suggest that reduced macronutrient and energy availability for metabolism and growth are not just the result of deficient dietary intake, but also may be caused by repeated exposure to pathogens.**
- **Effective interventions should focus on both providing sufficient nutrition and increasing sanitation, water quality, and hygiene.**

Acknowledgment

Sponsored by the Bill & Melinda Gates Foundation, Healthy Birth, Growth, and Development initiative.

References

1. Guerrant RL, Oriá RB, Moore SR, Oriá MO, Lima AA. Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutr Rev.* 2008;66(9):487-505.
2. Lunn PG. The impact of infection and nutrition on gut function and growth in childhood. *Proc Nutr Soc.* 2000;59(1):147-154.

Sponsored by the Healthy Birth, Growth, and Development (HBGD) initiative representing Discovery & Translational Sciences, Integrated Development, Integrated Delivery, Nutrition, Agriculture, Water, Sanitation & Hygiene, Maternal, Newborn & Child Health, Enteric & Diarrheal Diseases, and Pneumonia Program Strategy Teams. HBGD*ki* was conceived of and is directed by shasha.jumbe@gatesfoundation.org.