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Patient-Specific Inference of Average Glucose from Glycated Hemoglobin: Toward Personalized Diabetic Monitoring with Precision Laboratory Medicine

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Glycated hemoglobin (HbA1c) is the gold standard for monitoring chronic glucose control in diabetes, providing estimate for a patient's average plasma glucose concentration over the prior ∼120 days. Patients with elevated HbA1c have significantly increased risks of morbidity and mortality. Despite the clear link between high HbA1c, elevated average glucose (AG), and poor clinical outcomes, the relationship between average glucose and HbA1c is not fully understood. Some patients with identical HbA1c have average glucose levels that vary by 33\%, and some patients with the same average glucose have HbA1c levels that vary by 26\%. If we could control these sources of variation for individual patients, we could provide precise, personalized diabetic monitoring that would greatly improve patient outcomes for one of the largest healthcare burdens. We demonstrate here that RBC lifespan is the single most important source of variability in the HbA1c-AG relation.

We combine deterministic modeling of hemoglobin glycation (as first reported by Bunn et al. 1976) with stochastic modeling of the RBC lifespan variability (with measurements from Khera et al. 2015). The model is used to demonstrate the contributions of the measured variation in RBC lifespan to the variation in HbA1c in addition to contribution of average glucose.

By combining a biochemical model of glycation kinetics with a stochastic analysis of RBC lifespan variability, we can reconstruct the known linear regression relation between average plasma glucose level and measured HbA1c. Our results show consistency of the measured HbA1c and averaged glucose from the A1c-Derived Average Glucose (ADAG) Study Group (N=507, Nathan et al. 2008) with our model simulation. Data from the Diabetic Control and Complications Trial (N=1439, DCCT 1993) reveal similar consistency between the measurements and the model simulations. The model demonstrates that documented variability in the human RBC lifespan is sufficient to explain all of the observed variability in the relation between HbA1c and average glucose.

Our combined modeling of hemoglobin glycation and RBC lifespan variation strongly supports no significant difference in the glucose-independent glycation rate between individuals, because any differences in glycation rate would need to be almost perfectly anti-correlated with variability in the RBC lifespan for those individuals. We can use the model to estimate the patient's average RBC lifespan from a measurement of HbA1c and average glucose. This patient-specific estimate of RBC age can then be combined with future HbA1c measurements to provide more accurate estimate of average glucose and thus diabetic monitoring personalized for each individual patient.