Validation and implementation of low-cost dynamic insulin sensitivity tests

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AIM: To provide a low-cost insulin sensitivity test, while maintaining rich information content.

The dynamic insulin sensitivity and secretion test (DISST) was designed to capture insulin secretion kinetics and glucose dynamics with a less clinically intense protocol than the euglycaemic clamp (EIC), or IVGTT. DISTq was developed to enable real-time and low-cost identification of insulin sensitivity by using only glucose data. While the DISST directly measures the participant's insulin response to the test stimulus, DISTq estimates the response with a series of population-derived relationships

The DISST and EIC were undertaken by 50 heterogeneous participants and the insulin sensitivity values of the DISST, DISTq and EIC were compared

OUTCOMES: Correlation between the gold standard EIC and DISST and DISTq were R=0.81 and R=0.76, respectively

The DISST 50th percentile under-estimation of the EIC was -10.6% (IQR -26.8% to 7%), and ROC c-unit was 0.96. The 50th percentile over-estimation produced by DISTq was 13.4% (IQR -24.7 to 33.1%), and the ROC c-unit was 0.84. Participant tolerance of the DISST protocol was very high. No symptomatic hyperglycaemic incidents were noted.

The DISST was capable of distinguishing clinically important differences in insulin secretion that the EIC could not.

BARRIER TO UPTAKE: The DISST and DISTq parameter identification methods are sometimes considered too complex to apply.

Many groups with a primary focus on clinical research can lack access to parameter identification software or mathematical expertise. For the DISST or the DISTq to be used by such groups, some provision must be made for parameter identification.

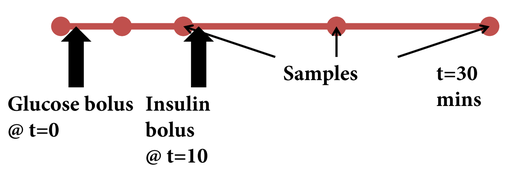
SOLUTION: A stand-alone, simple-to-use computer program could allow any research group to use the DISST or DISTq.

The Dynamic Insulin Sensitivity and Secretion Test (DISST)

Clinical protocol

The DISST is similar to the insulin-modified intravenous glucose tolerance test (IM-IVGTT) with some important distinctions:

- Uses comparatively low-dose to avoid saturation of insulin-mediated uptake of glucose [1, 2]
- Uses in-frequently sampled protocol with a lower overall duration
- Requires one skin puncture
- 5 samples are assayed for C-peptide as well as glucose and insulin



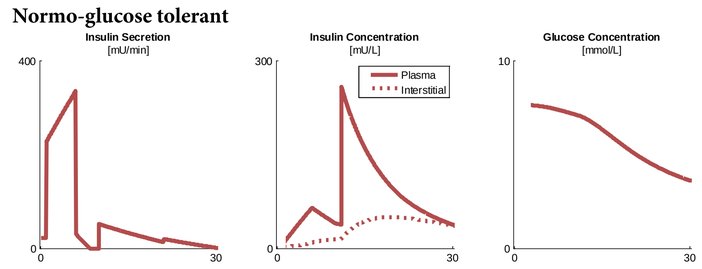
Modelling Strategy

The comparatively low clinical intensity of the DISST requires robust modelling and parameter identification approaches to obtain clinically relevant parameter values. In particular:

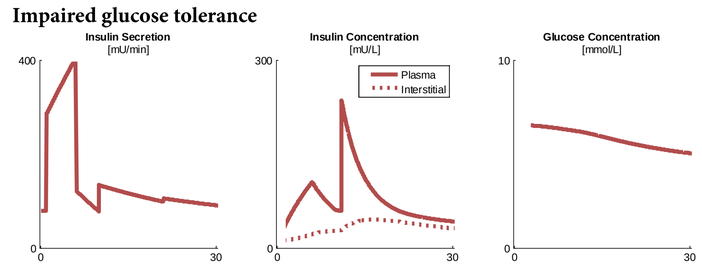
- C-peptide assays are used to obtain insulin secretion profiles using the deconvolution process of Van Cauter *et al.* [3]
- Insulin pharmacokinetics between the plasma and interstitium are directly modelled with additional resolution provided by insulin secretion profiles
- Glucose decay is modelled with a single parameter, insulin sensitivity, to maximise identification stability [4, 5]
- Parameter identification is undertaken by the iterative integral method [6, 7]

Typical DISST outcomes

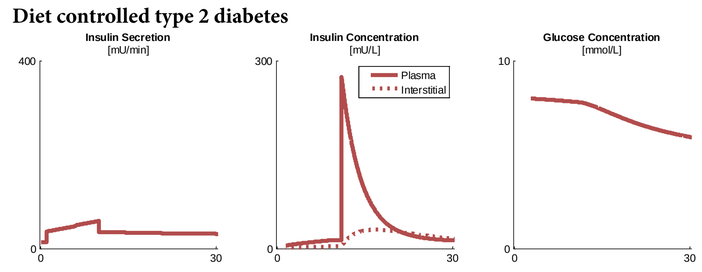
Normo-glucose tolerant



Impaired glucose tolerance



Diet controlled type 2 diabetes



The Quick Dynamic Insulin Sensitivity Test (DISTq)

DISTq does not use insulin or C-peptide assays, and thus must estimate the participant's insulinaemic response to the DISST test stimulus. There are no strong *a-priori* relationships for the factors that define insulin kinetics. However, these factors have relatively strong relationships with insulin sensitivity. Hence, the iterative process summarised in steps 1-5 allows convergence to an accurate insulin sensitivity value.

The process is explained thoroughly in Docherty *et al.* [6, 8]

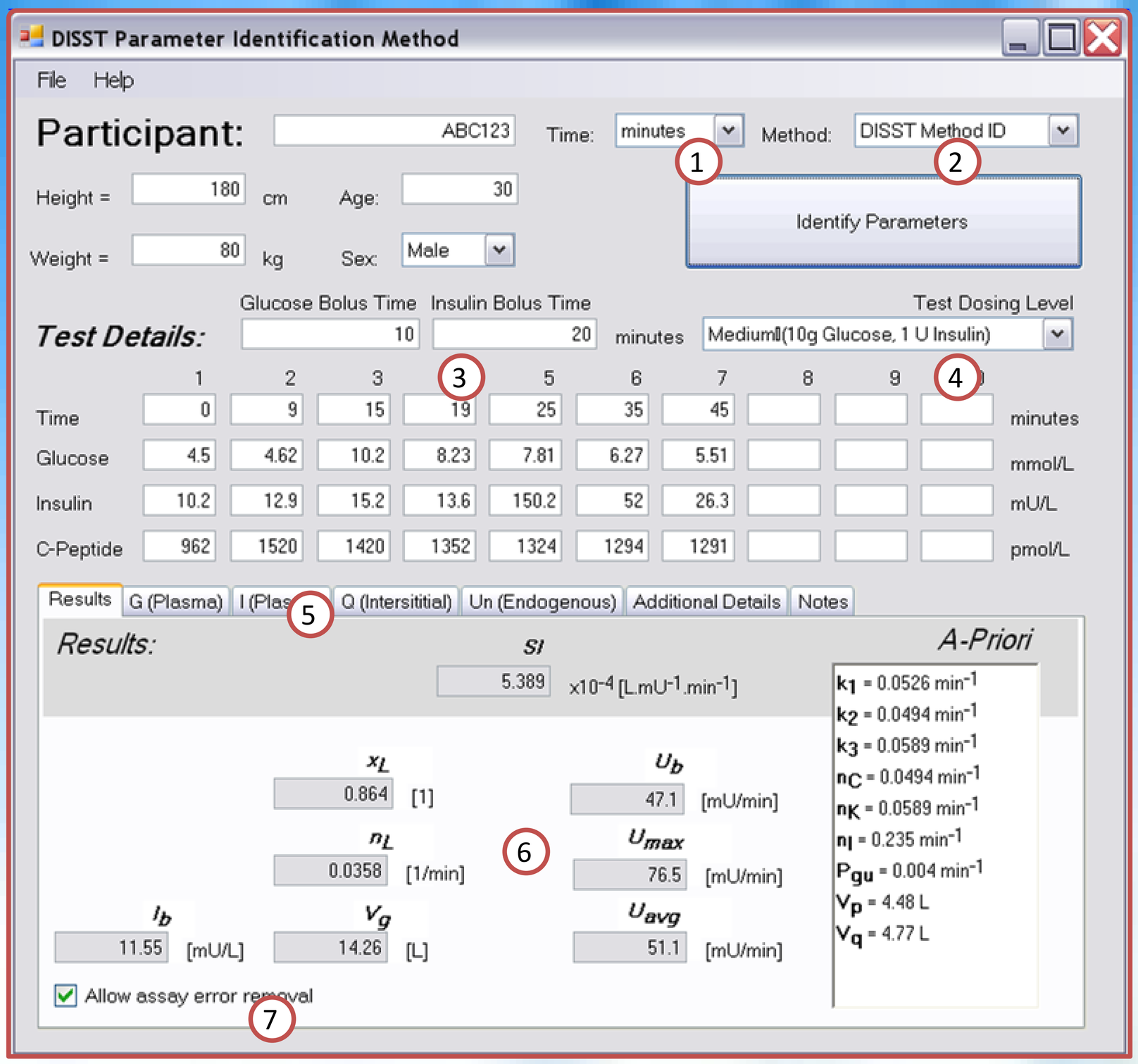
DISTq Parameter Identification

1. Define population average insulin sensitivity ($10_{x10^{-4}}$ L.mU^{-1}.min^{-1})
2. Estimate basal insulin, hepatic insulin clearance, and a pre-hepatic insulin secretion profile using estimated insulin sensitivity value and population-based equations
3. Simulate model-based interstitial insulin profile using estimated values
4. Identify insulin sensitivity with simulated interstitial insulin profile and measured glucose data
5. Iterate steps 2-4 updating insulin sensitivity until convergence

Hybrid Methods

DISST and DISTq represent two disparate methods of measuring insulin sensitivity from dynamic insulin sensitivity data. While the test stimulus is common between the methods, they have very different assay costs. Hence, a series of methods were proposed to provide a compromise between the distinct strategies of the DISST and the DISTq. These methods allow optimal test selection for a wide range of clinical applications [9, 10].

Finally the common protocol means that if a lower-resolution test response is too close to a clinical threshold, the samples taken can be re-assayed to allow a higher resolution test, without the need for an additional clinical protocol.



DISST ID program features

1. Can use minute or second resolution
2. Can recognise best parameter identification method for given input data. All of the methods presented in Docherty *et al.* [9, 10] can be used
3. Allows precise time input
4. Allows differing dosing
5. Provides plots of glucose concentration, insulin concentration and pre-hepatic insulin secretion
6. Outputs all participant specific estimated, *a-priori* and identified parameter values
7. Identifies assay error and can automatically ignore bad assays during parameter identification, if desired

- Results can be saved to csv
- Batch files can be processed

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