SOFTWARE TOOL ARTICLE

ogttMetrics: Data structures and algorithms for oral glucose tolerance tests [version 1; peer review: 1 approved with reservations]

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V1 First published: 16 May 2017, 6:684
<https://doi.org/10.12688/f1000research.11317.1>
Latest published: 16 May 2017, 6:684
<https://doi.org/10.12688/f1000research.11317.1>

Abstract

We describe an open source software package, *ogttMetrics*, to compute diverse measures of glucose metabolism derived from oral glucose tolerance tests (OGTTs). Tools are provided to organize, visualize and compare OGTT data from large cohorts. Numerical difficulties in estimation of parameters of the Bergman minimal model are described, and in one large clinical trial, the simpler closed form index of Matsuda is observed to lead to similar rankings of individuals with respect to insulin sensitivity, and similar inferences concerning effects of modifications to carbohydrate content and glycemic index of experimental diets.

Keywords

diabetes, carbohydrate metabolism, clinical trials, nonlinear models, multivariate analysis

Open Peer Review

Approval Status ?

1

version 1

16 May 2017

[view](#)

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the **RPackage** gateway.

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Competing interests: No competing interests were disclosed.

Grant information: This work was supported by US National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (5R21DK098720-02; V. Carey, PI), and National Cancer Institute (5U24 CA180996-04; M. Morgan, PI.)

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Stubbs BJ, Frankston K, Ramos M *et al.* **ogttMetrics: Data structures and algorithms for oral glucose tolerance tests [version 1; peer review: 1 approved with reservations]** F1000Research 2017, **6**:684
<https://doi.org/10.12688/f1000research.11317.1>

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Introduction

Disorders of carbohydrate metabolism contribute substantially to overall disease burden throughout the world. According to the International Diabetes Foundation ([International Diabetes Federation: IDF Diabetes Atlas, 2015](#)), over 400 million individuals are diabetic, and numbers afflicted continue to rise.

Various tests are used to diagnose diabetes or assess risk of diabetes. In the oral glucose tolerance test (OGTT), a specified quantity of glucose is ingested orally. Plasma concentrations of glucose and insulin are measured at specific times after ingestion. Panels (a) and (b) of [Figure 1](#) illustrate trajectories of glucose and insulin concentrations in a single patient performing the 120 minute protocol.

Methods for administering, analyzing, and clinically interpreting OGTT results are subjects of active research. Concerns with the use of individualized compartmental models for OGTT analysis are discussed in the work of [Theodorakis et al. \(2017\)](#). These authors propose population level nonlinear modeling for estimation of insulin sensitivity, and demonstrate that empirical Bayes procedures have desirable properties for computation and interpretation.

In this report, we describe an open-source software, *ogttMetrics*, for the management and analysis of OGTT series collected in large cohorts, and illustrate the application of models and metrics to a cross-over clinical trial ([Sacks et al. \(2014\)](#)) of effects of varying glycemic index and carbohydrate content of controlled diets. A widely cited proprietary software tool for fitting compartmental models to OGTT data is SAAM-II ([Barrett et al. \(1998\)](#)). We developed *ogttMetrics* to allow open investigation into properties of OGTT series, for which the SAAM-II models yield untenable estimates or do not converge. In addition, we saw an opportunity to develop a formal structure for collections of large numbers of OGTT series. We adopted the Bioconductor [MultiAssayExperiment](#) structure for this purpose, and introduced methods for interactive visualization and quality assessment of OGTT series, exploiting structures and functions of this package to simplify the coding.

Methods

Informal derivation of insulin sensitivity via the minimal model

Following [Bergman et al. \(1979\)](#), let $G(t)$ and $I(t)$ denote time-dependent plasma concentrations of glucose and insulin respectively. Various time-dependent factors affect the trajectories of these concentration functions, and we will assume that derivatives

Figure 1. Output of `plot_OGTT_fit` for a single OGTT series, from the baseline contribution of an OMNICarb participant. (a) The observed glucose concentrations (dots) and predictions (line). (b) Insulin concentrations (dots) and linear interpolation. (c) Predicted glucose vs. insulin action $X(t)$. (d) Rate of appearance of glucose, $Ra(t)$.

of these function with respect to time, and partial derivatives of these functions with respect to relevant time-dependent variables, can be defined. Let $\dot{G}$ denote the rate of change of glucose concentration in plasma over time. Glucose effectiveness is defined as $E = -\partial\dot{G}/\partial G$. This is described as “the quantitative enhancement of glucose disappearance due to an increase in the plasma glucose concentration” (Bergman *et al.*, 1979, p. E673). At steady state, insulin sensitivity is $S_I = \partial E/\partial I$. A four compartment model (model VI of Bergman *et al.* (1979)) leads to differential equations

$$G'(t) = (p_1 - X(t))G(t) + B_0$$

and

$$X'(t) = p_2 X(t) + p_3 I(t)$$

where $X(t)$ is an abstract time-dependent function representing insulin action, $G(t)$ is the time-dependent function representing glucose concentration, $I(t)$ represents time-dependent insulin concentration, and B_0 represents “glucose balance” (difference between rates of hepatic release to circulation and uptake in peripheral tissue) extrapolated to zero glucose concentration. By the definition of glucose effectiveness, the first differential equation implies $E(t) = X(t) - p_1$, and, at steady state, $X_{ss} = -I_{ss} p_3 / p_2$. This final expression is substituted into the expression for E just obtained, and after formal partial differentiation by I , we obtain $S_I = -p_3 / p_2$.

A formal specification

In the following,

- $G(t)$ is the plasma glucose concentration (mg/dl),
- $I(t)$ is the plasma insulin concentration (μ U/ml),
- G_b and I_b are the baseline values of glucose and insulin,
- $X(t)$ represents insulin action on glucose production and disposal (min^{-1}),
- S_I is insulin sensitivity ($\text{min}^{-1}/\mu\text{U} \cdot \text{ml}^{-1}$),
- p_2 is a rate constant for dynamics of insulin action (min^{-1}),
- $Ra(\alpha, t)$ denotes a time-dependent function representing appearance of glucose in plasma, with parameters α ($\text{mg} \cdot \text{min}^{-1}/\text{kg}$),
- V is volume of distribution (dl/kg), and
- S_G is glucose effectiveness per unit volume (min^{-1}).

We consider the specific formalism for the dalla Man *et al.* minimal model given by Burattini *et al.* (2006):

$$\frac{dG(t)}{dt} = -[S_G + X(t)] \cdot G(t) + S_G \cdot G_b + \frac{Ra(\alpha, t)}{V}$$

$$\frac{dX(t)}{dt} = -p_2 \cdot X(t) + p_2 \cdot S_I [I(t) - I_b],$$

with initial conditions $G(0) = G_b$ and $X(0) = 0$.

Estimation

The procedure of Dalla Man *et al.* (2002) involves two phases. In the first phase, the system of ordinary differential equations (ODE) above is solved on the basis of provisional settings of unknown parameters. The solution yields pointwise predictions of glucose concentrations $\hat{G}_i$ with t ranging over the sampling time course of the OGTT. In the second phase, parameters of the ODE system are updated using non-linear least squares. The phases are iterated until the sum of squared discrepancies $\sum_i (G_i - \hat{G}_i)^2$ converges to a minimum. Inputs to the algorithm are measured time series of glucose and insulin concentrations, and individual body weight; other quantities, such as glucose effectiveness (S_G), fraction of ingested dose absorbed (FA), and volume of distribution (V) are taken as fixed constants, with values derived from results of other experiments.

Programming considerations

The kernel of fitOneMinMod in the *ogttMetrics* package is

```
model <- function(t, Y, parameters) {
  with(as.list(parameters), {
    dy1 = -(Sg + Y[2]) * Y[1] + Sg * Gb + (ra(a1, a2,
      a3, t, BW, D, FA, DC)/V)
    dy2 = -p2 * Y[2] + p2 * SI * (Insulin(t) - Ib)
    list(c(dy1, dy2))
  })
}
```

Here the interface to *lsoda* in the *deSolve* package is employed (Hindmarsh, 1983; Petzold, 1983). The formal variables $Y[1]$ and $Y[2]$ represent $G(t)$ and $X(t)$ respectively; $ra()$ and $Insulin()$ are specially defined functions that return, for any given time in the course of the OGTT, the rate of glucose appearance, and insulin concentration, respectively. The *lsoda* solver is invoked in the function *mmsolfn*, whose inputs $a1$, $a2$, $a3$ are free parameters of a piecewise linear model for $Ra(t)$, the rate of appearance of glucose; input SI is the target quantity of interest, the measure of insulin sensitivity. The values of free parameters are obtained by minimizing the sum of squared differences between observed glucose g and values predicted by the ODE system for current values of the unknown parameters:

```
mmsolfn = function(a1, a2, a3, SI) lsoda(c(Gb,
0), t, model,
  c(a1 = a1, a2 = a2, a3 = a3, SI = SI))
fit = nls(g ~ mmsolfn(a1, a2, a3, SI)[, 2], start =
nlsinit,
  trace = nlstrace, control = fullNLScontrol)
```

Additional quantities BW , D , FA , DC are used to implement the constraint of Dalla Man *et al.* (2002)

$$\int_0^{420} Ra(t)dt = \frac{D \cdot FA}{BW}$$

in which BW is participant body weight, D is the dose of glucose ingested, and FA is the fraction of ingested glucose that is actually absorbed; DC is constant that determines the rate of exponential decay of glucose concentration in plasma past minute 120.

For concreteness, [Figure 1](#) displays all components of a minimal model fitted to a single 120 minute OGTT.

Data management and reporting

In practice, OGTT series can be collected according to different protocols and may include additional biomarkers such as c-peptide concentrations. For flexible data management and analysis, we adopted the data structure of the *MultiAssayExperiment* package of Bioconductor. We extended this structure in a class called `ogttCohort`, which includes metadata about timing of concentration measures. Each biomarker series for each individual is stored as a column of an R matrix, with rows and columns coordinated across assays. Arbitrary additional sample-level information can be linked to assay data. High level functions `getMinmodSIs` and `addMatsuda120` fit the minimal model or compute the Matsuda index for each series, and append results to the data container. Because the minimal model may be time-consuming to fit, support is provided for parallel computation of multiple models. Use of a compact formal representation of all the OGTT data collected on a cohort simplifies creation of generic reports and visualizations. [Figure 2](#) is based on the `QCplots` function, that can be applied to any `ogttCohort` instance. The top two panels display aspects of marginal (time-specific)

distributions using boxplots. The bottom two panels are views of joint distributions of features and samples using the biplot methodology of [Gabriel \(1971\)](#). Calibrated outlier detection, proceeding under the assumption that the OGTT series are multivariate normal with a common mean vector and unspecified covariance matrix, can be conducted for glucose and insulin series separately, using `mvOutliers`. The procedure of [Caroni & Prescott \(1992\)](#) is used.

Numerical considerations

[Theodorakis et al. \(2017\)](#) mentions that the standard (proprietary, closed source) software tool SAAM-II ([Barrett et al. \(1998\)](#)) failed to produce acceptable estimates of insulin sensitivity in over one-third of 106 samples. Similar difficulties were encountered in the OMNICarb study. These challenges motivated us to create an open source solution that would foster investigation of aspects of glucose and insulin series for which the minimal model fails to converge, and allow comparison of alternative metrics of carbohydrate metabolism on large datasets. [Figure 3](#) displays the `SIexplorer` interactive interface. Given a collection of OGTT results in an `ogttCohort` structure, the `SI vs Matsuda` panel shows the association between estimated SI, Matsuda's index, and convergence status of the Burattini et al. formulation

Figure 2. Output of `QCplots` for a sample of 50 observations from the OMNICarb study in the `obaSamp` object distributed with `ogttMetrics`. Top two panels are time-specific boxplots, bottom two are biplots based on principal components analysis of the 50x2 7-dimensional vectors of glucose and insulin concentrations in the dataset.

Figure 3. Slexplorer interactive display of association of insulin sensitivity, Matsuda index, and minimal model convergence with default settings.

of the minimal model. The display is made with transformed axes (log10 for SI, square root for Matsuda's index). Negative estimates of SI are Winsorized to the smallest positive estimate observed in the data. Positive correlation between the indices is apparent, and the general trend appears to be obeyed for the majority of estimates of SI for which the dalla Man *et al.*, algorithm does not converge.

Application to a cross-over trial

We created the *ogttMetrics* package to analyze data from the OMNIBarb study (Sacks *et al.* (2014)). This study involved over 150 overweight individuals ($BMI > 25 kg/m^2$) whose systolic blood pressure was in the interval 120–159 mmHg, or diastolic blood pressure in the interval 70–90 mmHg. Individuals with diagnoses of diabetes, cardiovascular disease, or chronic kidney disease were excluded. Four experimental diets were designed to provide contrasting values of overall carbohydrate content and glycemic index of foods consumed. Carbohydrate and glycemic index each had two levels denoted C and c (G and g) respectively, leading to the set (CG, Cg, cG, cg) of experimental diets. Each patient received a randomly ordered sequence of diets from this set, consuming each assigned diet for five weeks, with a pause of two weeks between diets. At the end of each feeding period a 120-minute OGTT protocol was administered. As noted previously, attempts to fit the Bergman minimal model with SAAM-II frequently failed to produce acceptable values, and so the study report of effects on insulin sensitivity used Matsuda's index. We have used the *ogttMetrics* package to structure the data and compute both Matsuda's index and the minimal model SI.

Figure 4 shows how the diet effects are estimated using these two indices. Confidence intervals are presented for five different contrasts. The left panel of Figure 4 is identical in content to the Insulin sensitivity panel of Figure 3 of Sacks *et al.* (2014). The right panel shows results based on SI that are qualitatively similar to those found with Matsuda's index, with the exception of the estimated effect of lowering glycemic index in the context of high overall carbohydrate content. With Matsuda's index, the 95% confidence interval excludes zero, but this is not observed when SI is used. Further work on optimizing estimation of insulin sensitivity from the 120 minute OGTT protocol is warranted; the empirical Bayes approach of Theodorakis *et al.* (2017) is of particular interest as individual-level estimation in that procedure borrows strength from information assembled for the cohort as a whole.

Installation and operation

Installation of *ogttMetrics* can be accomplished using R 3.4 via `devtools::install_github("vjcitn/ogttMetrics", dependencies=c("Depends", "Imports", "Suggests"))`. The key infrastructure components required for *ogttMetrics* are CRAN package *deSolve* for minimal model estimation, and Bioconductor package *MultiAssayExperiment* for data management. The *SIexplorer* utility employs the *shiny* package. These key components have extensive dependencies among other CRAN packages, but these dependencies are automatically resolved by the `install_github()` command given above. All example data analyzed or visualized in this paper are accessible using the `data()` function. For example, to reproduce

Figure 4. Left: Two-sided 95 percent confidence intervals for within-person diet contrasts based on Matsuda's index. Right: Analogous confidence intervals for within-person diet contrasts based on SI estimated using ogttMetrics.

Figure 1, use the commands `library(ogttMetrics); data(obaSamp); m1 = minmodByID(obaSamp, "1"); plot_OGTT_fit(m1)`. For Figure 2, in the same session, use `QCplots(obaSamp)`.

Users may import data managed in spreadsheets (CSV format) for use with this software. An executable example is available with `example(csvImport)`.

Conclusions

The reference assay for glucose metabolism is the hyperinsulinemic-euglycemic clamp (Soonthornpun *et al.* (2003)). Because it is less expensive and much less invasive, the OGTT is an attractive assay for assessing insulin sensitivity, particularly in large studies. We have presented, and made freely available (at <http://github.com/vjcitn/ogttMetrics>), a collection of data structures and functions in the R programming language that help manage and interpret OGTT series collected in cohort studies and clinical trials.

We and others have found that the minimal model frequently fails to generate reasonable values for SI in OGTT series encountered in practice. In part this is manifested in non-convergence of the basic nonlinear model for the glucose trajectory. However, we have not observed a striking disparity between rankings of participants using the estimate of SI based on an unsatisfactory minimal model fit, and rankings obtained when the closed form Matsuda index is computed on the same OGTT data (Figure 3, Spearman correlation between Matsuda and estimated SI = 0.5782, $p < .0001$). The estimated SI may be good enough for practical use, but further investigation of features of OGTT data associated with non-convergence of the minimal model, and biologically motivated elaborations of the model that yield successful fits more generally, should be undertaken.

The tools for multivariate analysis and interactive model visualization in the SIexplorer component of ogttMetrics will be useful for

gaining additional insight into subtyping of patients according to features of glucose and insulin trajectories.

Software and data availability

Software and all data analyzed in this paper are available from: <http://github.com/vjcitn/ogttMetrics>

Archived source code as at time of publication: DOI, [10.5281/zenodo.570174](https://doi.org/10.5281/zenodo.570174) (Carey, 2017)

License: GPL-3

Author contributions

Benjamin Stubbs and Keith Frankston developed software and visualizations, analyzed the data, and participated in manuscript development. Marcel Ramos developed the MultiAssayExperiment package of Bioconductor. Frank M. Sacks and Nancy Laranjo conceived and executed the OMNICarb study created the database from which ogttMetrics data are derived, and participated in manuscript development. Vincent Carey acquired funding for software development, developed software and visualizations, and wrote the manuscript.

Competing interests

No competing interests were disclosed.

Grant information

This work was supported by US National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (5R21DK098720-02; V. Carey, PI), and National Cancer Institute (5U24 CA180996-04; M. Morgan, PI.)

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Current Peer Review Status: ?

Version 1

Reviewer Report 01 June 2017

<https://doi.org/10.5256/f1000research.12213.r22802>

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The submission describes an open source R software package for managing, visualising and analysing data from oral glucose tolerance tests (OGTTs).

The aim of the work in providing open source tools for the analysis of OGTT data is highly commendable. From a technical standpoint, the package clearly follows good software development practices by using existing data management infrastructure and extensive automated testing. The authors make a strong effort to make the results reported in the paper reproducible by providing code for reproducing half of the figures. The package includes a vignette that provides some example workflows that seem potentially very useful.

While these basics are well covered, the package still has quite a few rough edges that may make it more difficult to adopt for potential end users. I believe these should be addressed to make the submission scientifically sound.

1. Installation of the package on a fresh R 3.4 according to instructions fails, presumably due to inability of `devtools::install_github()` to install required dependencies:

ERROR: dependencies 'S4Vectors', 'MultiAssayExperiment', 'Biobase', 'SummarizedExperiment', 'parody', 'ggbiplot' are not available for package 'ogttMetrics'

2. After manual install of the required Bioconductor packages, installation still fails because ggbiplot is not available in any standard repositories but only on GitHub.

3. Installing the package using suggested approach after a manual install of all missing dependencies seems to fail to install the vignette. (Not visible in the listing provided by vignette().)

4. Running the examples provided in the paper produces some errors:

```
> QCplots(obasamp)
Error in experiments(oc) : object 'obasamp' not found
```

After fixing the command the first run gives:

```
> QCplots(obaSamp)
...
Error in UseMethod("depth") :
  no applicable method for 'depth' applied to an object of class "NULL"
>
Oddly enough this works when used later.
```

5. Additionally, when reading the example from the PDF, the command `plot_OGTT_fit` contains 'fi' ligature which breaks copy-paste of the command from the PDF.

6. Running "R CMD check" produces notes and a warning, which probably would not be acceptable at the major repositories:

```
* checking for missing documentation entries ... WARNING
Undocumented data sets:
  'omnicCG_samp' 'omnicCG_samp' 'omniccg_samp'
All user-level objects in a package should have documentation entries.
See chapter 'Writing R documentation files' in the 'Writing R
Extensions' manual.
```

7. These fairly trivial technical issues aside, I am unsure what is the intended audience of the package and how useful it would be for that audience. The authors present a smooth workflow for analysing pre-packaged data from existing large studies, but instructions for importing new data are limited to one sparsely documented example and it is not immediately obvious how to e.g. compute the minimal models for this example. The vignette contains some code snippets that are likely relevant, but more comments and explanation would be needed. I tried a little but could not get this working easily. In general the vignette would need to be clearer to be useful to new users.

8. Related to the above note, the `csvImport` format should be documented better. The vignette could contain an example with different time points. A hard-coded default of time points seems difficult for something where there probably is no generally applicable default.

9. The minimal model code contains a number of magic constants with some assumed default values. It would be very good to document with proper references where these come from. It is especially unclear where the constant 420 in the integral in Programming considerations comes from and if that can be safely used for data with a different sampling period.

10. The implications of the piece-wise linear model using a different model before and after 120 min for data with different (either shorter or longer) sampling period and times should be discussed. Can the model be safely applied in these cases? Are there other hidden assumptions that could impact the end users?

11. The unit for BMI in "Application to a cross-over trial" is reported incorrectly ($25\text{kg}=\text{m}^2$, units

incorrectly in italics).

Further suggestions:

12. It is good that the code contains many stopifnot() sanity checks, but more informative error messages suggesting how to fix things would be useful for the end users.

13. The specification of the model might benefit from more consistent notation for derivatives. (Now sometimes d/dt , sometimes G' and X' .)

14. It would be good to include a copyright notice with author and license information to each source file. See <https://www.gnu.org/licenses/gpl-howto.html>

Is the rationale for developing the new software tool clearly explained?

Yes

Is the description of the software tool technically sound?

Partly

Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others?

Partly

Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool?

Yes

Are the conclusions about the tool and its performance adequately supported by the findings presented in the article?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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