Research Notes: Week 4

Maya Watanabe
Christina Catlett

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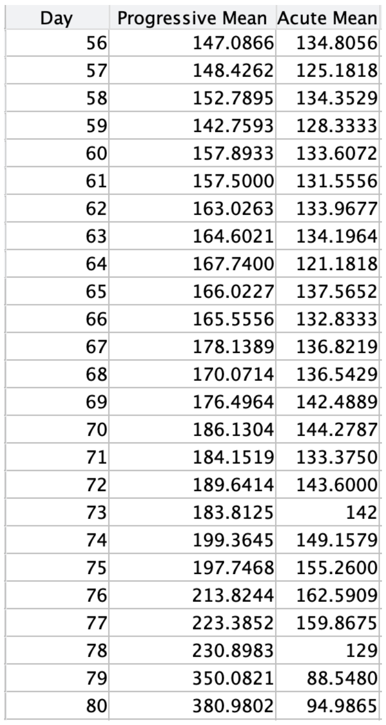
Drawing from our previous work, we spent this week transitioning from fitting the simple Lotka-Volterra system to fitting the 12-equation Type 1 diabetes system described in Shtylla et al. 2019. Delayed Rejection Adaptive Metropolis (DRAM) was used to fit the model's 53 parameters to mean glucose data collected by Matthews et al. 2015 in NOD mice. Additionally, global optimization methods began to be explored. Such methods are widely used and act as a good benchmark for checking the accuracy of parameter fits suggested by DRAM. Specifically, Particle Swarm Optimization (PSO) was examined.

1 Data

The data consisted of the mean glucose measurements of 400 mice over a period of 24 days prior to the onset of diabetes, as characterized by the increase of blood glucose levels past 250 mg/dl for two measurements in a row. Measurements were taken irregularly; with samples being taken every two days for all mice, and samples every 24 hours for mice exceeding the 250 mg/dl threshold. Ideally, we would be able to fit parameters to glucose readings from individual mice, but the dataset is missing a large number of values, and this became a clearly daunting task. To avoid the inconsistencies in the data, we decided instead to examine the mean of the glucose readings for two groups of mice: those with progressive T1D, and those with acute T1D. According to research notes from Mathew et al.:

"After data was taken, mice were classified according to the characteristics of their onset. If the mouse had steady euglycemia (glucose levels in the healthy range) before having a sudden onset of hyperglycemia, the mouse was categorized as having an acute form of the disease. Conversely, if the mouse simply had an 'excursion' above 200 mg/dL (meaning there was a reading of 200 or above, and at least one subsequent reading before diagnosis with diabetes was below this number), the diagnosis of the disease was categorized to be progressive."

Additionally, these data points had to be time-adjusted. Originally collected on a time frame relative to diabetes onset (i.e. starting at day -24 and progressing to day 0), they had to be altered to exist on linear, consecutive time. As data collection began when the mice were 8-weeks old, we adjusted days -24 to 0 to be days 56 to 80. This left us with the data shown in Figure 1 and plotted in Figure 2.



Day	Progressive Mean	Acute Mean
56	147.0866	134.8056
57	148.4262	125.1818
58	152.7895	134.3529
59	142.7593	128.3333
60	157.8933	133.6072
61	157.5000	131.5556
62	163.0263	133.9677
63	164.6021	134.1964
64	167.7400	121.1818
65	166.0227	137.5652
66	165.5556	132.8333
67	178.1389	136.8219
68	170.0714	136.5429
69	176.4964	142.4889
70	186.1304	144.2787
71	184.1519	133.3750
72	189.6414	143.6000
73	183.8125	142
74	199.3645	149.1579
75	197.7468	155.2600
76	213.8244	162.5909
77	223.3852	159.8675
78	230.8983	129
79	350.0821	88.5480
80	380.9802	94.9865

Figure 1: Mean glucose data for progressive and acute mice populations

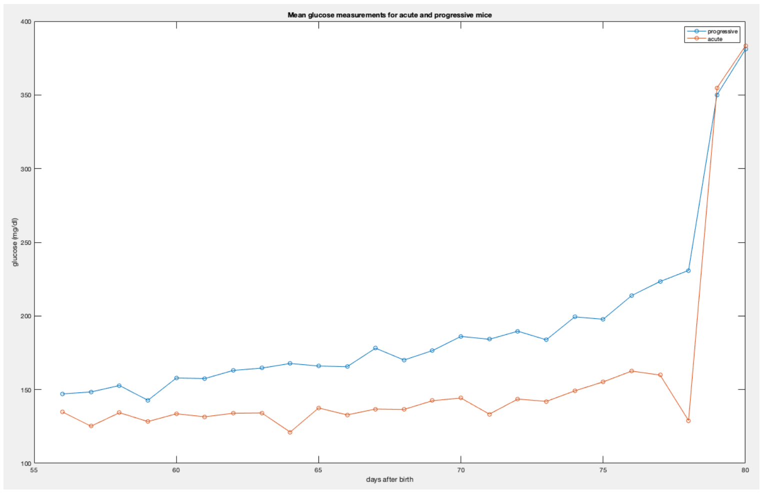


Figure 2: Mean glucose data for progressive and acute mice populations over days since birth.

2 Fitting with DRAM

As a refresher from last week, DRAM is an MCMC algorithm that combines the methods of the adaptive Metropolis and delayed rejection algorithms (outlined below).

2.1 Adaptive Metropolis

1. Sample parameter sets for a period of length k_0 where values are computed using an initial covariance matrix V_0

- k_0 is chosen to balance mixing with sufficient diversity of points to ensure a non-singular covariance matrix
- Shorter adaptation intervals tend to produce better mixing and high acceptance ratios; thus the chain is more responsive to new data
- In practice, k_0 is often 100

2. At the kth step of the chain, adaptation commences: the initial V_0 is updated to the covariance matrix, V_k

$$V_k = s_p cov(q^0, q^0, ..., q^{k-1}) + \epsilon I_p$$

- s_p is a design parameter that depends o the dimension (p) of the parameter space; a common choice is $s_p = 2.38^2/p$
- The term ϵI_p refers to an ID matrix of dimension p. It simply exists to ensure that V_k is positive definite. Often, $\epsilon = 0$

2.2 Delayed Rejection

In the standard Metropolis algorithm, when a candidate parameter set q^* is rejected (with its prescribed acceptance ratio), the current step parameter set, q^{k-1}, is retained and q^* is discarded before choosing the next sample. In the *delayed rejection* (DR) algorithm, when q^* is rejected, alternative candidates q^{*j} are constructed and considered instead of immediately reverting back to q^{k-1}. For example, q^{*2}, a second-stage candidate, is chosen using proposal function

$$J_2(q^{*2}|q^{k-1}, q^*) = N(q^{k-1}, \gamma_2^2 V_k)$$

- $V_k = R_k R_k^T$ is the covariance matrix produced in the adaptive algorithm
- $J_2(q^{*2}|q^{k-1}, q^*)$ indicates that we propose q^{*2} having started at q^{k-1} and rejected q^*
- $\gamma_2 < 1$ narrows the second-stage function and increases mixing

The acceptance criteria for the second-stage candidate is

$$\alpha_2(q^{*2}|q^{k-1}, q^*) = min(1, \frac{\pi(q^{*2}|v)J(q^*|q^{*2})[1-\alpha(q^*|q^{*2})]}{\pi(q^{k-1}|v)J(q^*|q^{k-1})[1-\alpha(q^*|q^{k-1})]})$$

The DRAM algorithm works as follows: Starting with parameter set q^{k-1}, we choose candidate sample q^*. If q^* is rejected, we propose candidate q^{*2}. If q^{*2} is rejected, we impose candidate q^{*3} and so on until we accept candidate q^{*j}. We begin sampling again with $q^{k-1} = q^{*j}$ as our current parameter set. After taking k samples, we update our covariance matrix (and thus our proposal distribution and acceptance ratio).

In the DRAM algorithm, the adaptive Metropolis and delayed rejection work together: AM updates the proposal via previously accepted candidates and the covariance matrix DR alters the proposal function to improve mixing.

Last week we focused on adapting DRAM to the Lotka-Volterra model. This week we adapted DRAM to the Type 1 Diabetes model.

2.3 Fitting the Type 1 Diabetes Model with DRAM

The Type 1 Diabetes model consists of a system of 12 differential equations (variables) and 53 parameters. Our DRAM algorithm allows us to parameterize the entire system even though glucose measurements are our only source of data. We began with a parameterization of the entire system to get a feel for how our algorithm would react to the increase in number of parameters and variables. After our discussion during the weekly meeting, a better approach would be to only fit parameters that are associated with the Glucose equation (we will attempt this next week). For now, we focus on the whole system.

2.3.1 Implementing the algorithm

The basic framework of our algorithm came from Marko Laine (found *here*) who parameterized a 3 equation, 20 parameter ODE system of algae. populations. The algorithm runs as follows:

1. *Load data*: see description above (Section 2)
2. *Set initial parameter values*: These values were loaded from the preset definitions given in Shtylla et al. 2019.
3. *Determine likelihood function*: Our sum of squares function takes the difference between the ode-solved data and the original data. In other words, it defines the error in the model. In this (and many scenarios), we assume that this error has a normal distribution.

```
%% Calculating model sum of squares
model.ssfun = @(theta, data) T1Dss(theta, data);
---------------------------------------------------
%% Sum-of-squares function
function ss = T1Dss(theta, data)
ydata=data(:,2); % original data

% Ynowave: no wave wild type (1)
% Ynnowave: NOD no wave (2)
% Ywave: wild type + wave (3)
% Ynwave: NOD + wave (4)
[~,ymodel]= T1Dfun(2); % uses Matlab ODE solver

ss = sum((ymodel-ydata).^2);
end
```

4. *Define the prior distribution*: When we know little about our parameters and model, we will assume a noninformative (uniform distribution) prior. Because we are supplied with individual differential equations, we can use the Matlab *fminsearch* function to determine a guess for the variance of our prior distribution. In this way, we are supplying our algorithm with a little more information about the sampling space of our parameters.

```
function [mse, params] = T1D_fitInitialParams(params, data)
% Extract the initial guess for your parameters (must be in vector form)
for i = 1:length(params)
    initGuess(i) = params{i}{2}; % value of parameter
    lb(i) = params{i}{3}; % lower bound of uniform prior
    ub(i) = params{i}{4}; % upper bound of uniform prior
end

%Run a quick fminsearch to get initial parameter and s2 guesses for DRAM
if length(data(:,1)) > length(params)
    fun = @(params) T1Dss(params, data); % solve ODE
    opt = optimset('Display', 'off');
    % Find minimum of constrained function
    [theta, ss0] = fmincon(fun, initGuess, [], [], [], [], lb, ub, [], opt);
    mse = ss0/(length(data(:,1))-length(params));

    %Now replace params starting values with fminsearch output
    for i = 1:length(params)
        params{i}{2} = theta(i);
    end
else
    mse = 1; % THIS MAY NEED TO BE CHANGED! Normal guess for mse breaks down! Need more
             % data pts than parameters
end
```

5. *Generating samples*: In this algorithm we run 2 DRAM chains. The first chain acts as the burn-in period. After this chain is completed, we take the final chain sample and use it as the initial chain values for our second chain, from which we actually collect and store parameter values.

```
%% Burn-in iterations
% First generate an initial chain.
options.nsimu = 1000; % number of iterations
options.method = 'dram'; % sampling method is DRAM
[results, chain, s2chain]= mcmcrun(model,data,params,options);

%% Running MCMC chain
% Then re-run starting from the results of the previous run,
options.nsimu = 5000;
options.method = 'dram';
[results, chain, s2chain] = mcmcrun(model,data,params,options, results); % note that the
% results of the first chain are an input of the second mcmcrun
```

6. *Results*
   - Plot parameter densities
   - Print mean parameter values
   - Check convergence via Geweke's diagnostic (convergence when mean of the first 10% = mean of the last 50% of the chain). Geweke value > 0.7 signals convergence
7. *Model Prediction*: This algorithm is also designed to plot predicted values of the model system using the parameter values sampled in the chain. Plotting these predictions tells us how much variability in the system our sampled parameters create; ideally we would want small variability which would tell us that our samples fit our model well.

2.3.2 Data/Model Options and Assumptions

Due to the various options of mouse data and ODE solver assumptions, there are many combinations of the model that we can run our algorithm on. We define the following combinations:

- NOD mouse + no wave + *simulated data*
- NOD mouse + no wave + *acute mouse data*
- NOD mouse + no wave + *progressive mouse data*
- NOD mouse + wave + *simulated data*
- NOD mouse + wave + *acute mouse data*
- NOD mouse + wave + *progressive mouse data*

Underlined options determine specific ODE solving assumptions and italicized options determine the different classifications of mouse data (see Section 2). Wave refers to the presence of the apoptotic β-cell wave.

We also only run our algorithm on the NOD mouse option because Mathews et al. 2015 mentions that they collected data only from NOD mice. We recognize however that we cannot be certain that this is true, so eventually we do plan to run our algorithm using the "wild-type" options as well.

Simulated data was generated by solving the ODE model (with and without wave) and adding normally distributed noise:

```
% Simulate 100 data points
[tmodel, ymodel]=T1D_dataSim(4); % ex. NOD mouse + no wave
% add normal noise
noise=normrnd(0,1,[1,100]);
data=[tmodel ymodel+noise'];
```

2.4 Results and Analysis

We ran our algorithm a total of 6 times. In this section we will illustrate the results of 1 of the 6 combinations that we ran our DRAM algorithm with and provide analysis. The rest of the results should be analyzed in the same fashion. To view full result figures please see *Appendix*. Here we view and analyze the DRAM performance on NOD mice + no wave + simulated data as this appears to be the "best" (or more accurate with the least variation) run.

We look first at the density plots produced by the algorithm, Figure 3.

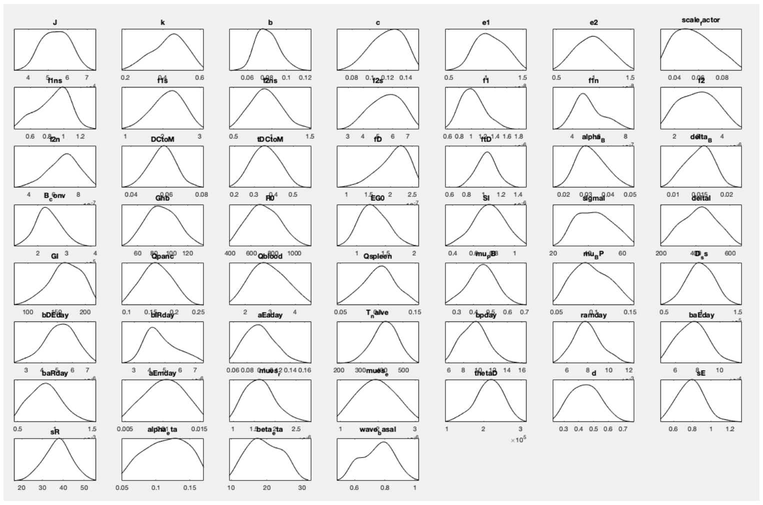
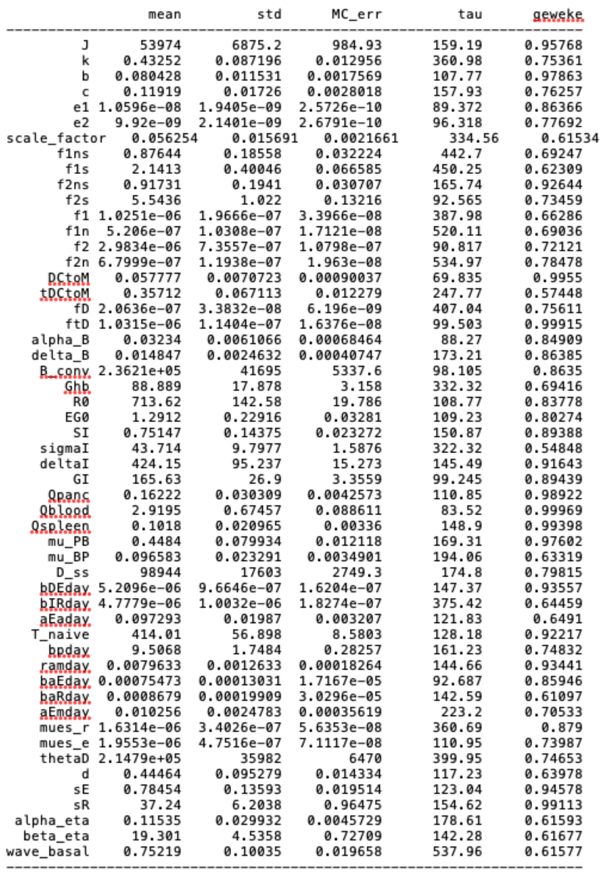


Figure 3: Parameter posterior density functions (pdfs) plots (53) for NOD mouse + no wave + simulated data.

From this figure we can see that the parameter pdfs look, for the most part, smooth with a single mode. This gives us a general indication that our algorithm is running correctly, as we would like our density functions to be smooth and continuous (although it may be that some parameters distributions are multi-modal).

Next we look at the information produced by our chain, namely the mean parameter values and Geweke's diagnostic for convergence, Figure 4.



```
                  mean         std      MC_err         tau      geweke
----------------------------------------------------------------------
          J      53974      6875.2      984.93      159.19     0.95768
          k    0.43252    0.087196    0.012956      360.98     0.75361
          b   0.080428    0.011531   0.0017569      107.77     0.97863
          c    0.11919     0.01726   0.0028018      157.93     0.76257
         e1 1.0596e-08  1.9405e-09  2.5726e-10      89.372     0.86366
         e2   9.92e-09  2.1401e-09  2.6791e-10      96.318     0.77692
scale_factor   0.056254    0.015691   0.0021661      334.56     0.61534
       f1ns    0.87644     0.18558    0.032224       442.7     0.69247
        f1s     2.1413     0.40046    0.066585      450.25     0.62309
       f2ns    0.91731      0.1941    0.030707      165.74     0.92644
        f2s     5.5436       1.022     0.13216      92.565     0.73459
         f1 1.0251e-06  1.9666e-07  3.3966e-08      387.98     0.66286
        f1n  5.206e-07  1.0308e-07  1.7121e-08      520.11     0.69036
         f2 2.9834e-06  7.3557e-07  1.0798e-07      90.817     0.72121
        f2n 6.7999e-07  1.1938e-07   1.963e-08      534.97     0.78478
      DCtoM   0.057777   0.0070723  0.00090037      69.835      0.9955
     tDCtoM    0.35712    0.067113    0.012279      247.77     0.57448
         fD 2.0636e-07  3.3832e-08   6.196e-09      407.04     0.75611
        ftD 1.0315e-06  1.1404e-07  1.6376e-08      99.503     0.99915
    alpha_B    0.03234   0.0061066  0.00068464       88.27     0.84909
    delta_B   0.014847   0.0024632  0.00040747      173.21     0.86385
     B_conv 2.3621e+05       41695      5337.6      98.105      0.8635
        Ghb     88.889      17.878       3.158      332.32     0.69416
         R0     713.62      142.58      19.786      108.77     0.83778
        EG0     1.2912     0.22916     0.03281      109.23     0.80274
         SI    0.75147     0.14375    0.023272      150.87     0.89388
     sigmaI     43.714      9.7977      1.5876      322.32     0.54848
     deltaI     424.15      95.237      15.273      145.49     0.91643
         GI     165.63        26.9      3.3559      99.245     0.89439
      Qpanc    0.16222    0.030309   0.0042573      110.85     0.98922
     Qblood     2.9195     0.67457    0.088611       83.52     0.99969
    Qspleen     0.1018    0.020965     0.00336       148.9     0.99398
      mu_PB     0.4484    0.079934    0.012118      169.31     0.97602
      mu_BP   0.096583    0.023291   0.0034901      194.06     0.63319
       D_ss      98944       17603      2749.3       174.8     0.79815
     bDEday 5.2096e-06  9.6646e-07  1.6204e-07      147.37     0.93557
     bIRday 4.7779e-06  1.0032e-06  1.8274e-07      375.42     0.64459
     aEaday   0.097293     0.01987    0.003207      121.83      0.6491
    T_naive     414.01      56.898      8.5803      128.18     0.92217
      bpday     9.5068      1.7484     0.28257      161.23     0.74832
     ramday  0.0079633   0.0012633  0.00018264      144.66     0.93441
     baEday 0.00075473  0.00013031  1.7167e-05      92.687     0.85946
     baRday  0.0008679  0.00019909  3.0296e-05      142.59     0.61097
     aEmday   0.010256   0.0024783  0.00035619       223.2     0.70533
     mues_r 1.6314e-06  3.4026e-07  5.6353e-08      360.69       0.879
     mues_e 1.9553e-06  4.7516e-07  7.1117e-08      110.95     0.73987
     thetaD 2.1479e+05       35982        6470      399.95     0.74653
          d    0.44464    0.095279    0.014334      117.23     0.63978
         sE    0.78454     0.13593    0.019514      123.04     0.94578
         sR      37.24      6.2038     0.96475      154.62     0.99113
  alpha_eta    0.11535    0.029932   0.0045729      178.61     0.61593
   beta_eta     19.301      4.5358     0.72709      142.28     0.61677
 wave_basal    0.75219     0.10035    0.019658      537.96     0.61577
----------------------------------------------------------------------
```

Figure 4: Table with details of the DRAM chain for NOD mouse + no wave + simulated data.

From this table, we can see that for a majority of the parameters our chain did converge with Geweke > 0.7. The best outcome would be for the chain to converge for all parameters, but given the number of parameters and the fact that we only have glucose measurement data, we are not sure how feasible this will be. The parameter means are useful for comparison of methods. For example, we plan to use the means produced by DRAM and PSO (Section 3) to compare the consistency and accuracy of each method.

Lastly, we can use our algorithm to predict what the model will do in the future given the parameter values sampled in the chain, Figure 5.

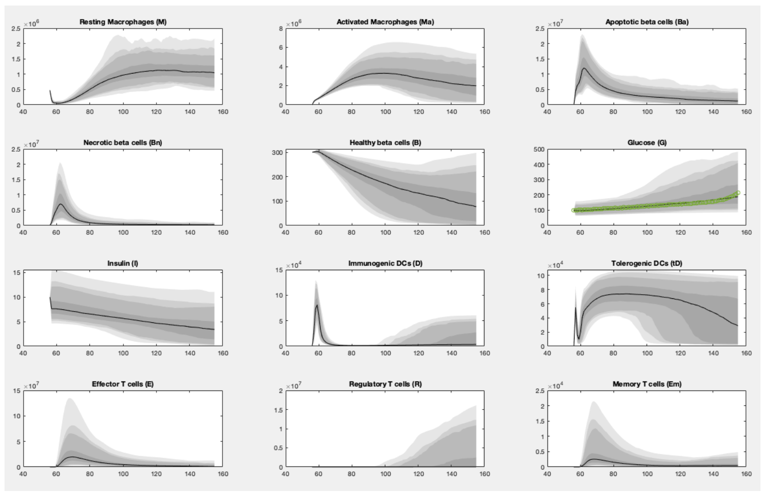


Figure 5: Predicted models for the NOD mouse + no wave + simulated data.

Here it is important to note that the overlapping gray shapes represent different predictions of the model based on individual parameter values that were taken from the results of our completed DRAM chain. Ideally we would like the range of these predictions to be small as that tells us our DRAM-ed parameter values fall in a smaller range, fit the model well, and produce little variation. It is easier to determine a "best" parameter value (for use in computations or other algorithms, models etc.) from a small rather than a large range of values.

2.4.1 Comments on results

It is important to note that at the moment we are unable to produce the predicted model figure for the DRAM combinations *with wave* (see Appendix: Fig. 12-14).

We would also note that, in general, the model predictions for acute and progressive mouse data without wave, are highly variable. This tells us that our parameter values are creating a lot of variation between predictions (see Appendix: Fig. 10 and 11). We are planning to investigate this issue further.

2.5 Improvements

We would like to run all our combinations again (plus those that incorporate the "wild-type" mouse data) on a subset of parameters. Instead of trying to fit all 53 parameters, it would be more useful to parameterize those which are included in and associated with the equation for Glucose (as this is the data we have). We hope to see better convergence of parameters as well as smaller variation in our models prediction as a result.

3 Fitting with PSO

3.1 What is PSO?

Particle Swarm Optimization (PSO) is global optimization algorithm serving to locate the global minimum of a function, known as the objective function. Like MCMC, the algorithm works iteratively to propose candiate solutions, measure the quality of these proposals according to the objective function, and adjust future proposals based on the outcome. The algorithm's development was based on a flock of birds hunting for food. As the birds fly, each bird is looking for food. Each bird knows where the best food source it has seen is, and it can listen to the squawks of others to determine their findings. If another bird has found a better food source than this bird has ever seen, it will likely change its flight path to investigate what that other bird has found. Otherwise, it will continue to explore, but also move towards its best discovered food source. All in all, as this process progresses, this leads to the flock localizing to one area, the one with the optimum food. Putting this mathematically, the algorithm is as follows:

1. Initialize a particle swarm of size n by selecting points ('particles') according to i˜Uniform(X_{min}, X_{max}) where X_{min}, X_{max} represent the lower and upper bounds of the search space, respectively
   (a) Assign each particle, i's, initial position as its personal best at time t: $P^t_{best,i}$
   (b) Determine the global best with $G_{best} = min(P^t_{best,i})$ for all i
2. Initialize parameters c_1 and c_2, acceleration parameters that determine a particle's attraction to its own findings and the findings of others, respectively
3. Begin the process of simulating the swarm by calculating the velocity vector for each particle i in each dimension j:

$$v^{t+1}_{ij} = v^t_{ij} + c_1 r^t_1[P^t_{best,i} - x^t_{ij}] + c_2 r^t_2[G^t_{best,i} - x^t_{ij}]$$

   where r represents a uniform random values $(0, 1)$
4. Update the location of each particle:

$$x^{t+1}_i = x^t_i + v^{t+1}_i$$

5. Recalculate P_{best} and G_{best} by evaluating the objective function for each x_i:
   - P_{best} = best location found by particle i
   - G_{best} = best location found by all particles
6. Repeat velocity and position updates until either the maximum number of iterations is reached, or the spread of the swarm is negligible (minimum threshold set before PSO begins)

This process is well-summarized in the following flowchart.

3.2 PSO Implementation

PSO was used to fit the 53 parameters of the T1D system to the data in Figure 1. MATLAB includes a built-in implementation of PSO in the Global Optimization Toolbox, thus that was used.

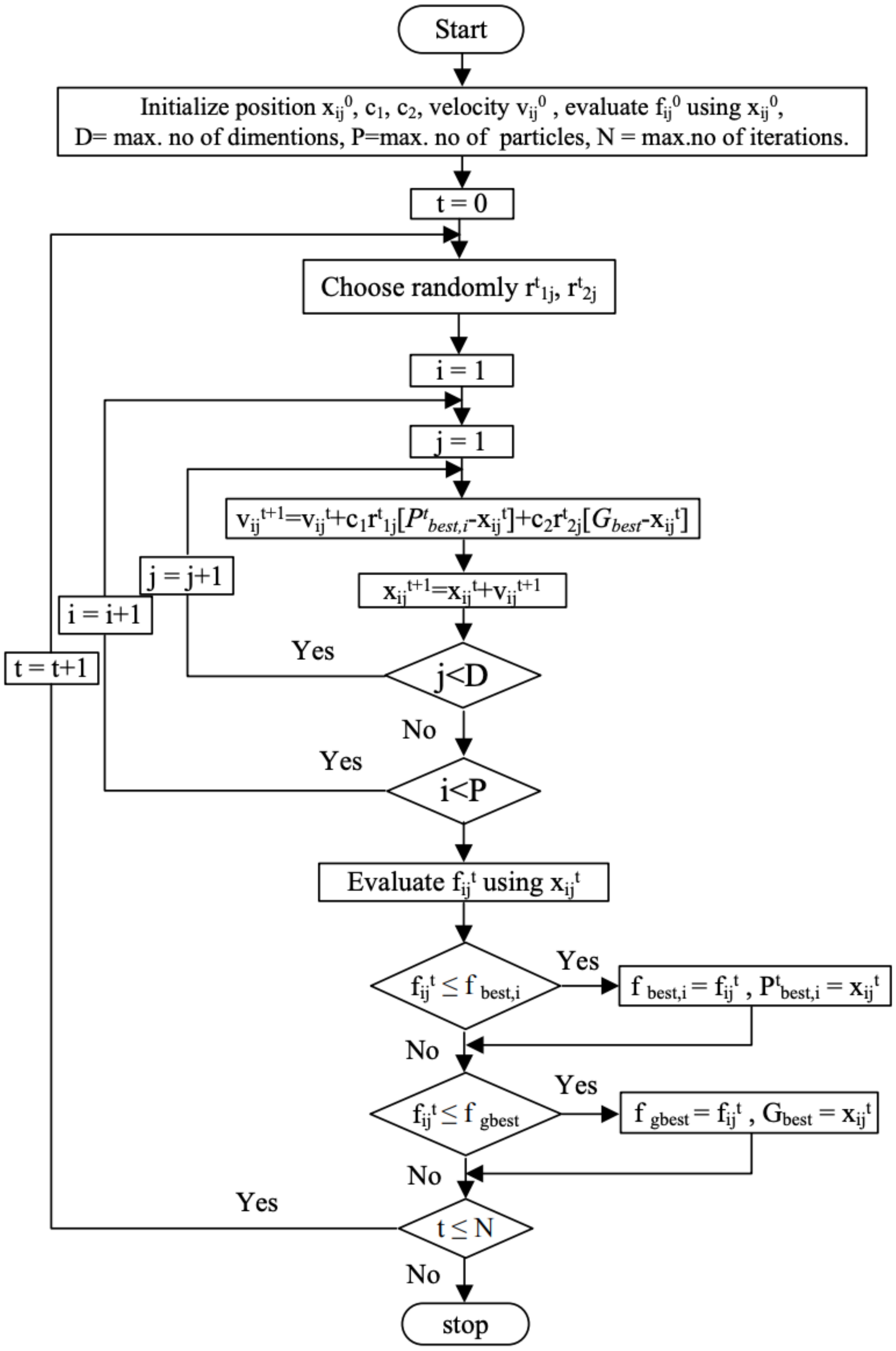
3.2.1 Parameter fitting

In order to adapt PSO to fit parameters to the model, an appropriate objective function needed to be chosen. As the objective function is minimized in PSO, a function that would decrease when a better parameter set is proposed needed to be implemented. The most simple function to fit this requirement was a simple sum-of-squares functions measuring the difference of the model outputs of the glucose equation in the T1D system and the observed data at analogous time points. This technique is not a new one; a similar choice as made for the likelihood function in the Metropolis-Hastings implementation of the Lotka-Volterra system in Week 3. By using the parameters in this equation as the state variables, a potential parameter set can be evaluated for fit, meaning that as this sum-of-squares decreases, the fit becomes better.

3.2.2 Options

Many options exist in the MATLAB implementation of PSO itself: coefficients c_1 and c_2 can be specified, as well as swarm size, allowable neighborhood, and maximum number of iterations. In our implementation, coefficients were set to default values by MATLAB, the neighborhood was not restricted (global best), a swarm size of 40 was selected, and the maximum number of iterations were set to 400. From research, swarm sizes of 20-60 tend to give both accurate and efficient results (as runtime increases with swarm size), so a midpoint value of 40 was chosen. The choice of 400 iterations stemmed from example code parameterizing a similarly-sized system.

To address the different categories in the data, as well as different events allowable in the model, the PSO process as provided several other options. First, regarding the data, the model could be run on NOD



Start
Initialize position x_{ij}^0, c_1, c_2, velocity v_{ij}^0 , evaluate f_{ij}^0 using x_{ij}^0,
D= max. no of dimentions, P=max. no of particles, N = max.no of iterations.
$t = 0$
Choose randomly r^t_{1j}, r^t_{2j}
$i = 1$
$j = 1$
$v_{ij}^{t+1}=v_{ij}^t+c_1r^t_{1j}[P^t_{best,i}-x_{ij}^t]+c_2r^t_{2j}[G_{best}-x_{ij}^t]$
$x_{ij}^{t+1}=x_{ij}^t+v_{ij}^{t+1}$
$j = j+1$
$i = i+1$
$t = t+1$
Yes
$j<D$
No
Yes
$i<P$
Evaluate f_{ij}^t using x_{ij}^t
$f_{ij}^t \leq f_{best,i}$
Yes
$f_{best,i} = f_{ij}^t$, $P^t_{best,i} = x_{ij}^t$
No
$f_{ij}^t \leq f_{gbest}$
Yes
$f_{gbest} = f_{ij}^t$, $G_{best} = x_{ij}^t$
No
Yes
$t \leq N$
No
stop

Figure 6: PSO Flowchart

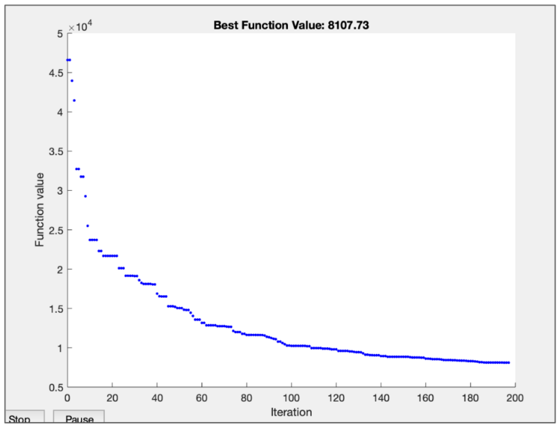
or wild type mice. In this case, different versions of parameters are used based on mouse type, so the unused parameters were removed from optimization. Though this feature is included, it is not used as all the mice in the data set are of the NOD variety. In a similar fashion, the model could be parameterized with and without the apoptotic wave occurring. This would set the parameters regarding the wave to 0 for the entirety of the optimization process as well as run the model with the correct options provided to the ODE solver for the apoptotic wave. Additionally, the system provides a set of initial conditions to the ODE solver based on the Topp healthy rest state for beta cells, glucose, and insulin. To account for biological differences in mice, all non-zero elements within the initial conditions vector can be optionally treated as parameters for the model.

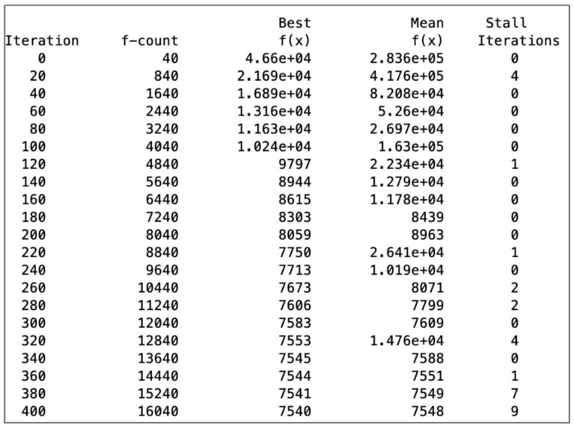
3.2.3 Assumptions

Besides baseline assumptions about the model being appropriate for the data, the largest assumption was in the allowable ranges for each of the parameters. Again based on example code for a similarly-sized system, the decision was made to allow guessing in an interval above and below an initial guess (the original parameters in the model). The size of this interval was determined to be ±50%‘for system parameters and ±15% for initial conditions. These numbers are fairly arbitrary, however, and were largely determined through trial and error. When run, if the optimal model parameters fell directly on upper/lower bounds, the spread of the interval was increased. The bounds on the initial conditions were tighter because it is assumed that the mouse is initially in a healthy state; we wanted our variation just to capture the natural biological different between mice, and a 50% interval would be much too large to remain within the healthy zone.

3.3 Results

During the run of the PSO function, three outputs are produced: a graph of the objective function's value at each iteration of the algorithm, a table printed in the command window containing information and the swarm at intermittent intervals, and a final set of optimized parameters. Below is an example of the graph and chart for the model run on the NOD progressive data. Additionally shown below are the optimal fits





```
                             Best           Mean      Stall
Iteration     f-count        f(x)           f(x)    Iterations
    0            40      4.66e+04      2.836e+05        0
   20           840     2.169e+04      4.176e+05        4
   40          1640     1.689e+04      8.208e+04        0
   60          2440     1.316e+04       5.26e+04        0
   80          3240     1.163e+04      2.697e+04        0
  100          4040     1.024e+04       1.63e+05        0
  120          4840          9797      2.234e+04        1
  140          5640          8944      1.279e+04        0
  160          6440          8615      1.178e+04        0
  180          7240          8303           8439        0
  200          8040          8059           8963        0
  220          8840          7750      2.641e+04        1
  240          9640          7713      1.019e+04        0
  260         10440          7673           8071        2
  280         11240          7606           7799        2
  300         12040          7583           7609        0
  320         12840          7553      1.476e+04        4
  340         13640          7545           7588        0
  360         14440          7544           7551        1
  380         15240          7541           7549        7
  400         16040          7540           7548        9
```

Figure 7: Output of MATLAB's PSO implementation

produced when running the model on the following combinations of data and model preferences (clockwise from top left):

1. NOD mice + Progressive mice data + no wave + constant ICs
2. NOD mice + Progressive mice data + wave + constant ICs
3. NOD mice + Progressive mice data + no wave + variable ICs
4. NOD mice + Progressive mice data + wave + variable ICs

The fits, as anticipated, look very similar between the combinations. Even when plotted on the same graph, the results appear almost identical. Though this may appear to be the case, it is in fact not, as the sum-of-squares function evaluated for each optimal set is slightly different. It becomes clear that the inclusion of the initial conditions within the optimization process leads to a better fit, and that the inclusion of the wave does not impact the fit of the model in any recognizable way.

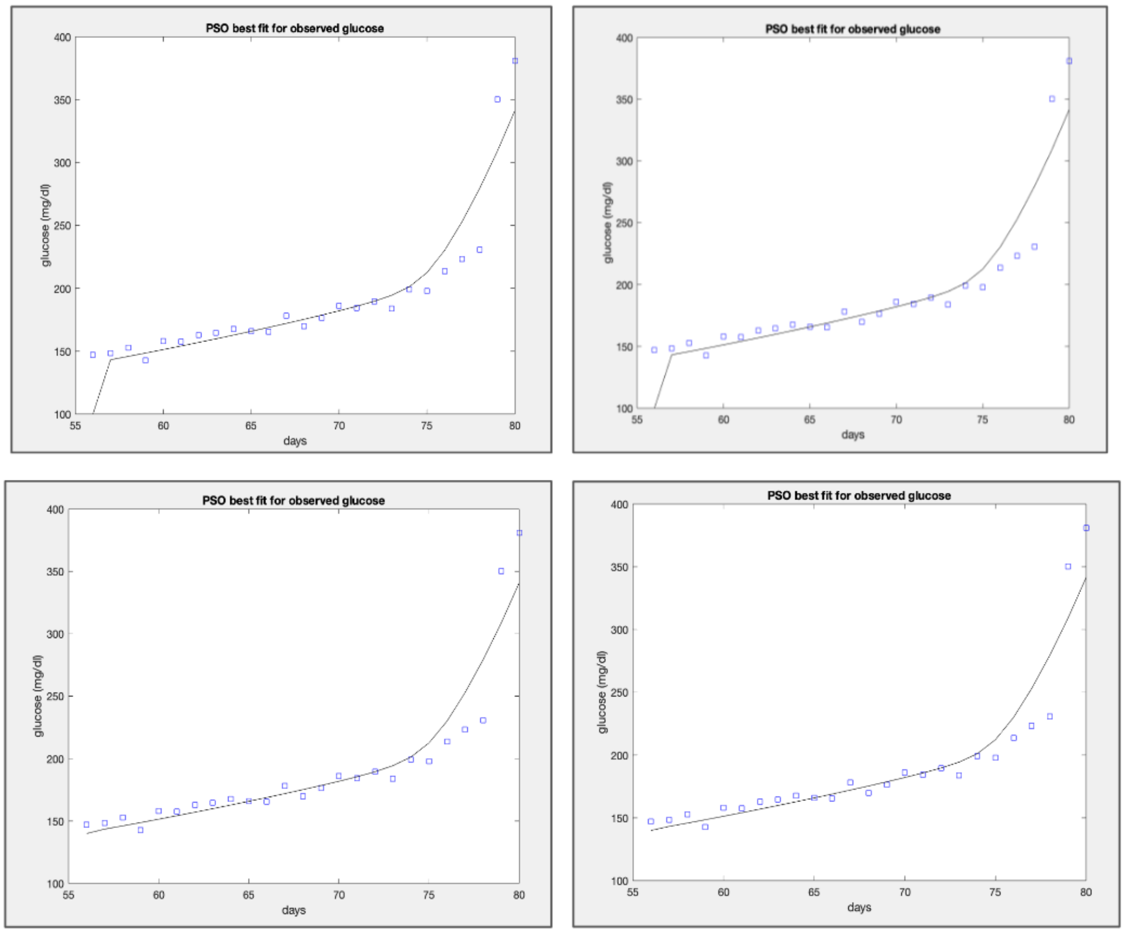


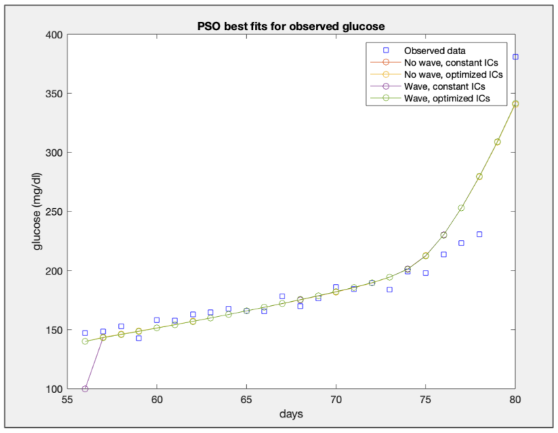
Figure 8: Best fit to model, data combinations for progressive mice

3.4 Improvements

To improve the biological applicability of this particular implementation of PSO, tightening the upper and lower bounds would be very helpful. The biological limits on certain parameters were not known, so the interval decided is not well-informed. Additionally, using more metrics to quantify how well the model fits the data would be beneficial over a visual inspection. Finally, all parameters were optimized in the work above. By incorporating more knowledge about the system by setting certain, non-sensitive parameters constant, the sensitive parameters can be optimized more carefully. From previous work done on the model with sensitivity analyses, these parameters can be identified.

4 Next Steps

Knowing that our methods are functional, we would like to work towards running both DRAM and PSO on the raw Mathews et al. data rather than the mean values. This requires extensive cleaning and organization



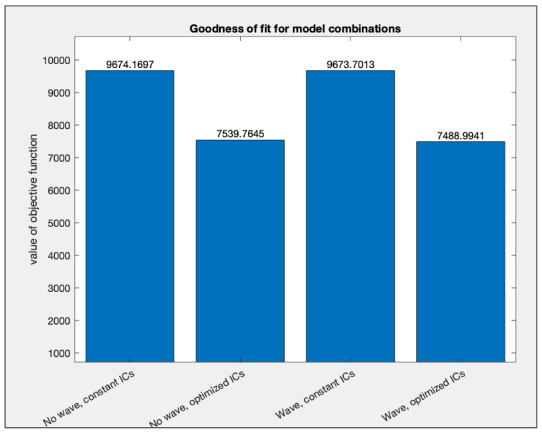
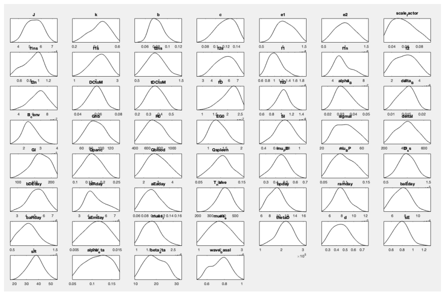


Figure 9: Comparison of fits

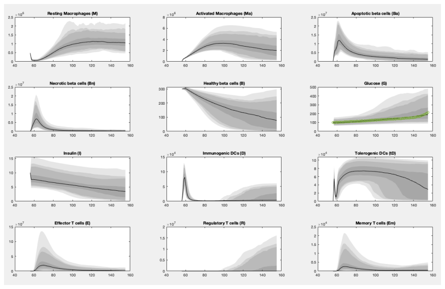
of the data, however, so we anticipate much time will need to spent on this, and effective interpolation strategies developed. Also, we made certain assumptions regarding the timespan of the data, so it would be nice to figure out a systematic way to organize the data to match the collection procedures described by Mathews.

5 Appendix

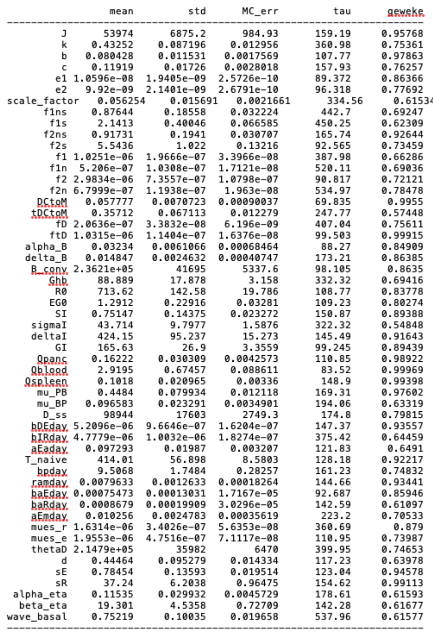
The following figures are illustrate the results of the DRAM algorithm. For better view of these results visit our *GitHub repository*.



(a) Parameter density plots



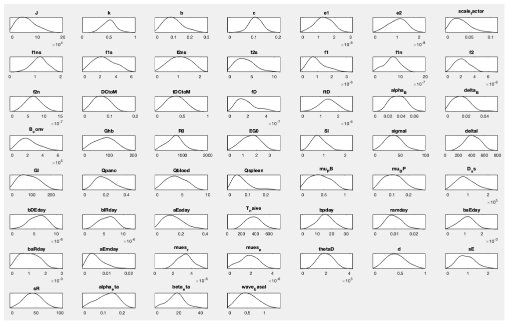
(b) Model prediction based on chain samples (per model variable). Original glucose data is overlaid in green.



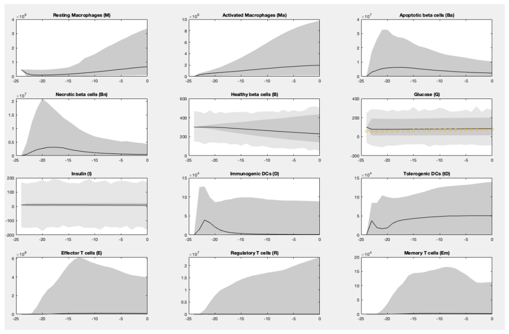
```
                  mean        std       MC_err        tau     geweke
--------------------------------------------------------------------
           J      53974     6875.2      984.93     159.19    0.95768
           k    0.43252   0.087196    0.012956     360.98    0.75361
           b   0.080428   0.011531   0.0017569     107.77    0.97863
           c    0.11919    0.01726   0.0028018     157.93    0.76257
          e1 1.0596e-08 1.9405e-09  2.5726e-10     89.372    0.86366
          e2   9.92e-09 2.1401e-09  2.6791e-10     96.318    0.77692
scale_factor   0.056254   0.015691   0.0021661     334.56    0.61534
        f1ns    0.87644    0.18558    0.032224      442.7    0.69247
         f1s     2.1413    0.40046    0.066585     450.25    0.62309
        f2ns    0.91731     0.1941    0.030707     165.74    0.92644
         f2s     5.5436      1.022     0.13216     92.565    0.73459
          f1 1.0251e-06 1.9666e-07  3.3966e-08     387.98    0.66286
         f1n  5.206e-07 1.0308e-07  1.7121e-08     520.11    0.69036
          f2 2.9834e-06 7.3557e-07  1.0798e-07     90.817    0.72121
         f2n 6.7999e-07 1.1938e-07   1.963e-08     534.97    0.78478
       DCtoM   0.057777  0.0070723  0.00090037     69.835     0.9955
      tDCtoM    0.35712   0.067113    0.012279     247.77    0.57448
          fD 2.0636e-07 3.3832e-08   6.196e-09     407.04    0.75611
         ftD 1.0315e-06 1.1404e-07  1.6376e-08     99.503    0.99915
     alpha_B    0.03234  0.0061066  0.00068464      88.27    0.84909
     delta_B   0.014847  0.0024632  0.00040747     173.21    0.86385
      B_conv 2.3621e+05      41695      5337.6     98.105     0.8635
         Ghb     88.889     17.878       3.158     332.32    0.69416
          R0     713.62     142.58      19.786     108.77    0.83778
         EG0     1.2912    0.22916     0.03281     109.23    0.80274
          SI    0.75147    0.14375    0.023272     150.87    0.89388
      sigmaI     43.714     9.7977      1.5876     322.32    0.54848
      deltaI     424.15     95.237      15.273     145.49    0.91643
          GI     165.63       26.9      3.3559     99.245    0.89439
       Qpanc    0.16222   0.030309   0.0042573     110.85    0.98922
      Qblood     2.9195    0.67457    0.088611      83.52    0.99969
     Qspleen     0.1018   0.020965     0.00336      148.9    0.99398
       mu_PB     0.4484   0.079934    0.012118     169.31    0.97602
       mu_BP   0.096583   0.023291   0.0034901     194.06    0.63319
        D_ss      98944      17603      2749.3      174.8    0.79815
      bDEday 5.2096e-06 9.6646e-07  1.6204e-07     147.37    0.93557
      bIRday 4.7779e-06 1.0032e-06  1.8274e-07     375.42    0.64459
      aEaday   0.097293    0.01987    0.003207     121.83     0.6491
     T_naive     414.01     56.898      8.5803     128.18    0.92217
       bpday     9.5068     1.7484     0.28257     161.23    0.74832
      ramday  0.0079633  0.0012633  0.00018264     144.66    0.93441
      baEday 0.00075473 0.00013031  1.7167e-05     92.687    0.85946
      baRday  0.0008679 0.00019909  3.0296e-05     142.59    0.61097
      aEmday   0.010256  0.0024783  0.00035619      223.2    0.70533
      mues_r 1.6314e-06 3.4026e-07  5.6353e-08     360.69      0.879
      mues_e 1.9553e-06 4.7516e-07  7.1117e-08     110.95    0.73987
      thetaD 2.1479e+05      35982        6470     399.95    0.74653
           d    0.44464   0.095279    0.014334     117.23    0.63978
          sE    0.78454    0.13593    0.019514     123.04    0.94578
          sR      37.24     6.2038     0.96475     154.62    0.99113
   alpha_eta    0.11535   0.029932   0.0045729     178.61    0.61593
    beta_eta     19.301     4.5358     0.72709     142.28    0.61677
  wave_basal    0.75219    0.10035    0.019658     537.96    0.61577
--------------------------------------------------------------------
```

(c) Table showing mean parameter values and convergence criteria Geweke. We consider Geweke > 0.7 to have converged.

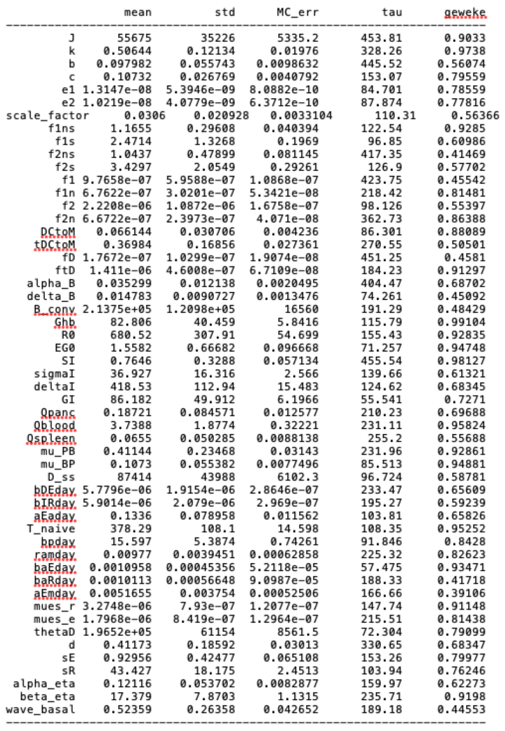
Figure 10: Results of DRAM on NOD mouse + no wave + simulated glucose data.



(a) Parameter density plots



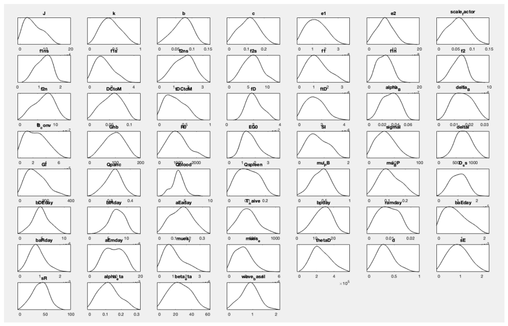
(b) Model prediction based on chain samples (per model variable). Original glucose data is overlaid in yellow.



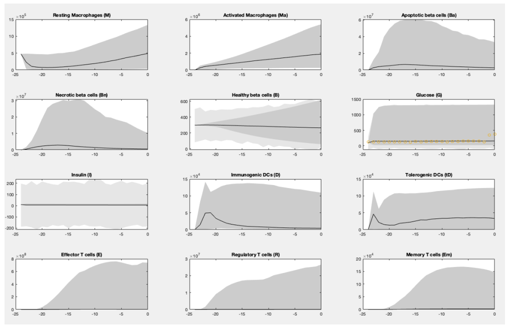
```
                   mean          std       MC_err          tau      geweke
--------------------------------------------------------------------------
          J       55675        35226       5335.2       453.81      0.9033
          k     0.50644      0.12134      0.01976       328.26      0.9738
          b    0.097982     0.055743    0.0098632       445.52     0.56074
          c     0.10732     0.026769    0.0040792       153.07     0.79559
         e1 1.3147e-08   5.3946e-09   8.0882e-10       84.701     0.78559
         e2 1.0219e-08   4.0779e-09   6.3712e-10       87.874     0.77816
scale_factor      0.0306     0.020928    0.0033104       110.31     0.56366
       f1ns      1.1655      0.29608     0.040394       122.54      0.9285
        f1s      2.4714       1.3268       0.1969        96.85     0.60986
       f2ns      1.0437      0.47899     0.081145       417.35     0.41469
        f2s      3.4297       2.0549      0.29261        126.9     0.57702
         f1 9.7658e-07   5.9588e-07   1.0868e-07       423.75     0.45542
        f1n 6.7622e-07   3.0201e-07   5.3421e-08       218.42     0.81481
         f2 2.2208e-06   1.0872e-06   1.6758e-07       98.126     0.55397
        f2n 6.6722e-07   2.3973e-07    4.071e-08       362.73     0.86388
      DCtoM    0.066144     0.030706     0.004236       86.301     0.88089
     tDCtoM     0.36984      0.16856     0.027361       270.55     0.50501
         fD 1.7672e-07   1.0299e-07   1.9074e-08       451.25      0.4581
        ftD  1.411e-06   4.6008e-07   6.7109e-08       184.23     0.91297
    alpha_B    0.035299     0.012138    0.0020495       404.47     0.68702
    delta_B    0.014783    0.0090727    0.0013476       74.261     0.45092
     B_conv 2.1375e+05   1.2098e+05        16560       191.29     0.48429
        Ghb      82.806       40.459       5.8416       115.79     0.99104
         R0      680.52       307.91       54.699       155.43     0.92835
        EG0      1.5582      0.66682     0.096668       71.257     0.94748
         SI      0.7646       0.3288     0.057134       455.54     0.98127
     sigmaI      36.927       16.316        2.566       139.66     0.61321
     deltaI      418.53       112.94       15.483       124.62     0.68345
         GI      86.182       49.912       6.1966       55.541      0.7271
      Qpanc     0.18721     0.084571     0.012577       210.23     0.69688
     Qblood      3.7388       1.8774      0.32221       231.11     0.95824
    Qspleen      0.0655     0.050285    0.0088138        255.2     0.55688
      mu_PB     0.41144      0.23468      0.03143       231.96     0.92861
      mu_BP      0.1073     0.055382    0.0077496       85.513     0.94881
       D_ss       87414        43988       6102.3       96.724     0.58781
     bDEday 5.7796e-06   1.9154e-06   2.8646e-07       233.47     0.65609
     bIRday 5.9014e-06    2.079e-06    2.969e-07       195.27     0.59239
     aEaday      0.1336     0.078958     0.011562       103.81     0.65826
    T_naive      378.29        108.1       14.598       108.35     0.95252
      bpday      15.597       5.3874      0.74261       91.846      0.8428
     ramday     0.00977    0.0039451   0.00062858       225.32     0.82623
     baEday   0.0010958   0.00045356   5.2118e-05       57.475     0.93471
     baRday   0.0010113   0.00056648   9.0987e-05       188.33     0.41718
     aEmday   0.0051655     0.003754   0.00052506       166.66     0.39106
     mues_r 3.2748e-06     7.93e-07   1.2077e-07       147.74     0.91148
     mues_e 1.7968e-06    8.419e-07   1.2964e-07       215.51     0.81438
     thetaD 1.9652e+05        61154       8561.5       72.304     0.79099
          d     0.41173      0.18592      0.03013       330.65     0.68347
         sE     0.92956      0.42477     0.065108       153.26     0.79977
         sR      43.427       18.175       2.4513       103.94     0.76246
  alpha_eta     0.12116     0.053702    0.0082877       159.97     0.62273
   beta_eta      17.379       7.8703       1.1315       235.71      0.9198
 wave_basal     0.52359      0.26358     0.042652       189.18     0.44553
--------------------------------------------------------------------------
```

(c) Table showing mean parameter values and convergence criteria Geweke. We consider Geweke > 0.7 to have converged.

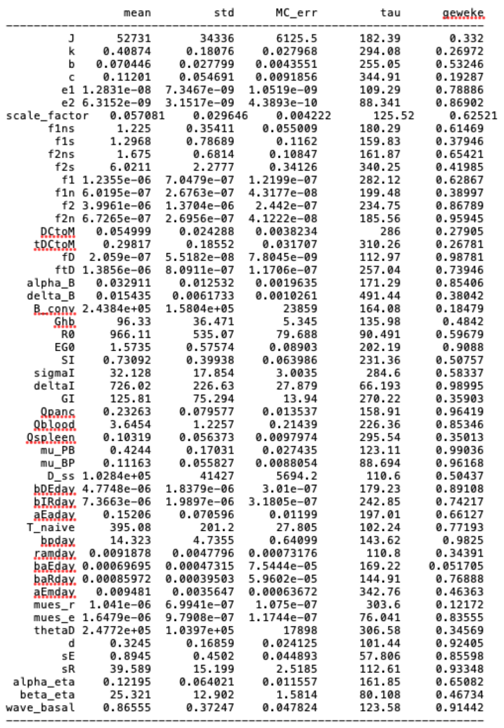
Figure 11: Results of DRAM on NOD mouse + no wave + acute mouse data.



(a) Parameter density plots



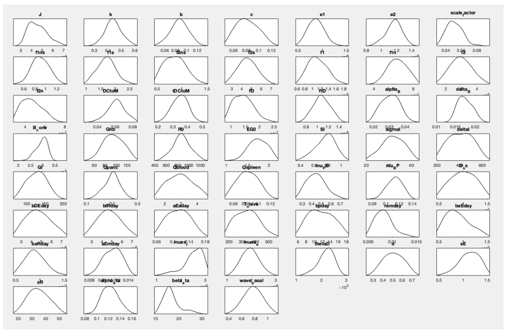
(b) Model prediction based on chain samples (per model variable). Original glucose data is overlaid in yellow.



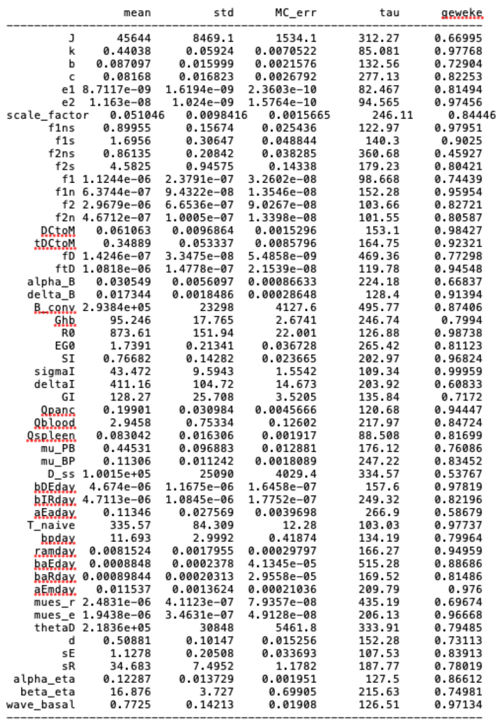
```
                   mean          std      MC_err         tau      geweke
-----------------------------------------------------------------------
          J       52731        34336      6125.5      182.39       0.332
          k     0.40874      0.18076    0.027968      294.08     0.26972
          b    0.070446     0.027799   0.0043551      255.05     0.53246
          c     0.11201     0.054691   0.0091856      344.91     0.19287
         e1  1.2831e-08   7.3467e-09  1.0519e-09      109.29     0.78886
         e2  6.3152e-09   3.1517e-09  4.3893e-10      88.341     0.86902
scale_factor    0.057081     0.029646    0.004222      125.52     0.62521
       f1ns       1.225      0.35411    0.055009      180.29     0.61469
        f1s      1.2968      0.78689      0.1162      159.83     0.37946
       f2ns       1.675       0.6814     0.10847      161.87     0.65421
        f2s      6.0211       2.2777     0.34126      340.25     0.41985
         f1  1.2355e-06   7.0479e-07  1.2199e-07      282.12     0.62867
        f1n  6.0195e-07   2.6763e-07  4.3177e-08      199.48     0.38997
         f2  3.9961e-06   1.3704e-06   2.442e-07      234.75     0.86789
        f2n  6.7265e-07   2.6956e-07  4.1222e-08      185.56     0.95945
      DCtoM    0.054999     0.024288   0.0038234         286     0.27905
     tDCtoM     0.29817      0.18552    0.031707      310.26     0.26781
         fD   2.059e-07   5.5182e-08  7.8045e-09      112.97     0.98781
        ftD  1.3856e-06   8.0911e-07  1.1706e-07      257.04     0.73946
    alpha_B    0.032911     0.012532   0.0019635      171.29     0.85406
    delta_B    0.015435    0.0061733   0.0010261      491.44     0.38042
     B_conv  2.4384e+05   1.5804e+05       23859      164.08     0.18479
        Ghb       96.33       36.471       5.345      135.98      0.4842
         R0      966.11       535.07      79.688      90.491     0.59679
        EG0      1.5735      0.57574     0.08903      202.19      0.9088
         SI     0.73092      0.39938    0.063986      231.36     0.50757
     sigmaI      32.128       17.854      3.0035       284.6     0.58337
     deltaI      726.02       226.63      27.879      66.193     0.98995
         GI      125.81       75.294       13.94      270.22     0.35903
      Qpanc     0.23263     0.079577    0.013537      158.91     0.96419
     Qblood      3.6454       1.2257     0.21439      226.36     0.85346
    Qspleen     0.10319     0.056373   0.0097974      295.54     0.35013
      mu_PB      0.4244      0.17031    0.027435      123.11     0.99036
      mu_BP     0.11163     0.055827   0.0088054      88.694     0.96168
       D_ss  1.0284e+05        41427      5694.2       110.6     0.50437
     bDEday  4.7748e-06   1.8379e-06    3.01e-07      179.23     0.89108
     bIRday  7.3663e-06   1.9897e-06  3.1805e-07      242.85     0.74217
     aEaday     0.15206     0.070596     0.01199      197.01     0.66127
    T_naive      395.08        201.2      27.805      102.24     0.77193
      bpday      14.323       4.7355     0.64099      143.62      0.9825
     ramday   0.0091878    0.0047796  0.00073176       110.8     0.34391
     baEday  0.00069695   0.00047315  7.5444e-05      169.22    0.051705
     baRday  0.00085972   0.00039503  5.9602e-05      144.91     0.76888
     aEmday    0.009481    0.0035647  0.00063672      342.76     0.46363
     mues_r   1.041e-06   6.9941e-07   1.075e-07       303.6     0.12172
     mues_e  1.6479e-06   9.7908e-07  1.1744e-07      76.041     0.83555
     thetaD  2.4772e+05   1.0397e+05       17898      306.58     0.34569
          d      0.3245      0.16859    0.024125      101.44     0.92405
         sE      0.8945       0.4502    0.044893      57.806     0.85598
         sR      39.589       15.199      2.5185      112.61     0.93348
  alpha_eta     0.12195     0.064021    0.011557      161.85     0.65082
   beta_eta      25.321       12.902      1.5814      80.108     0.46734
 wave_basal     0.86555      0.37247    0.047824      123.58     0.91442
-----------------------------------------------------------------------
```

(c) Table showing mean parameter values and convergence criteria Geweke. We consider Geweke > 0.7 to have converged.

Figure 12: Results of DRAM on NOD mouse + no wave + progressive mouse data.



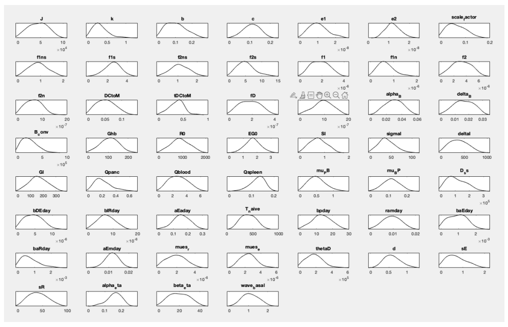
(a) Parameter density plots



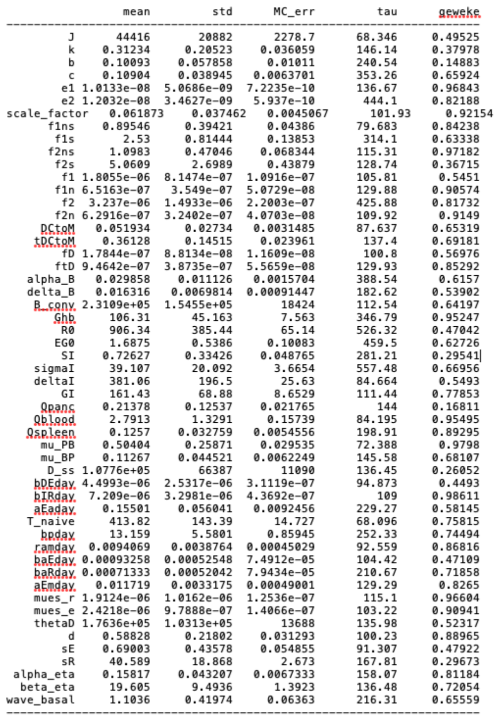
```
                   mean         std      MC_err         tau      geweke
-------------------------------------------------------------------------
           J       45644      8469.1      1534.1      312.27     0.66995
           k     0.44038     0.05924   0.0070522      85.081     0.97768
           b    0.087097    0.015999   0.0021576      132.56     0.72904
           c     0.08168    0.016823   0.0026792      277.13     0.82253
          e1 8.7117e-09  1.6194e-09  2.3603e-10      82.467     0.81494
          e2  1.163e-08   1.024e-09  1.5764e-10      94.565     0.97456
scale_factor    0.051046   0.0098416   0.0015665      246.11     0.84446
        f1ns     0.89955     0.15674    0.025436      122.97     0.97951
         f1s      1.6956     0.30647    0.048844       140.3      0.9025
        f2ns     0.86135     0.20842    0.038285      360.68     0.45927
         f2s      4.5825     0.94575     0.14338      179.23     0.80421
          f1 1.1244e-06  2.3791e-07  3.2602e-08      98.668     0.74439
         f1n 6.3744e-07  9.4322e-08  1.3546e-08      152.28     0.95954
          f2 2.9679e-06  6.6536e-07  9.0267e-08      103.66     0.82721
         f2n 4.6712e-07  1.0005e-07  1.3398e-08      101.55     0.80587
      DCtoM    0.061063   0.0096864   0.0015296       153.1     0.98427
     tDCtoM     0.34889    0.053337   0.0085796      164.75     0.92321
          fD 1.4246e-07  3.3475e-08  5.4858e-09      469.36     0.77298
         ftD 1.0818e-06  1.4778e-07  2.1539e-08      119.78     0.94548
     alpha_B    0.030549   0.0056097  0.00086633      224.18     0.66837
     delta_B    0.017344   0.0018486  0.00028648       128.4     0.91394
      B_conv 2.9384e+05       23298      4127.6      495.77     0.87406
         Ghb      95.246      17.765      2.6741      246.74      0.7994
          R0      873.61      151.94      22.001      126.88     0.98738
         EG0      1.7391     0.21341    0.036728      265.42     0.81123
          SI     0.76682     0.14282    0.023665      202.97     0.96824
      sigmaI      43.472      9.5943      1.5542      109.34     0.99959
      deltaI      411.16      104.72      14.673      203.92     0.60833
          GI      128.27      25.708      3.5205      135.84      0.7172
       Qpanc     0.19901    0.030984   0.0045666      120.68     0.94447
      Qblood      2.9458     0.75334     0.12602      217.97     0.84724
     Qspleen    0.083042    0.016306    0.001917      88.508     0.81699
       mu_PB     0.44531    0.096883    0.012881      176.12     0.76086
       mu_BP     0.11306    0.011242   0.0018089      247.22     0.83452
        D_ss 1.0015e+05       25090      4029.4      334.57     0.53767
      bDEday  4.674e-06  1.1675e-06  1.6458e-07       157.6     0.97819
      bIRday 4.7113e-06  1.0845e-06  1.7752e-07      249.32     0.82196
      aEaday     0.11346    0.027569   0.0039698       266.9     0.58679
     T_naive      335.57      84.309       12.28      103.03     0.97737
       bpday      11.693      2.9992     0.41874      134.19     0.79964
      ramday   0.0081524   0.0017955  0.00029797      166.27     0.94959
      baEday   0.0008848   0.0002378  4.1345e-05      515.28     0.88686
      baRday  0.00089844  0.00020313  2.9558e-05      169.52     0.81486
      aEmday    0.011537   0.0013624  0.00021036      209.79       0.976
      mues_r 2.4831e-06  4.1123e-07  7.9357e-08      435.19     0.69674
      mues_e 1.9438e-06  3.4631e-07  4.9128e-08      206.13     0.96668
      thetaD 2.1836e+05       30848      5461.8      333.91     0.79485
           d     0.50881     0.10147    0.015256      152.28     0.73113
          sE      1.1278     0.20508    0.033693      107.53     0.83913
          sR      34.683      7.4952      1.1782      187.77     0.78019
   alpha_eta     0.12287    0.013729    0.001951       127.5     0.86612
    beta_eta      16.876       3.727     0.69905      215.63     0.74981
  wave_basal      0.7725     0.14213     0.01908      126.51     0.97134
-------------------------------------------------------------------------
```

(b) Table showing mean parameter values and convergence criteria Geweke. We consider Geweke > 0.7 to have converged.

Figure 13: Results of DRAM on NOD mouse + wave + simulated mouse data.



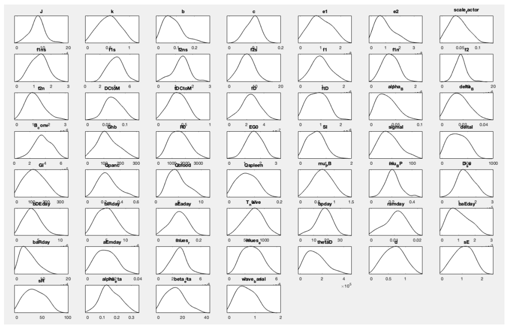
(a) Parameter density plots



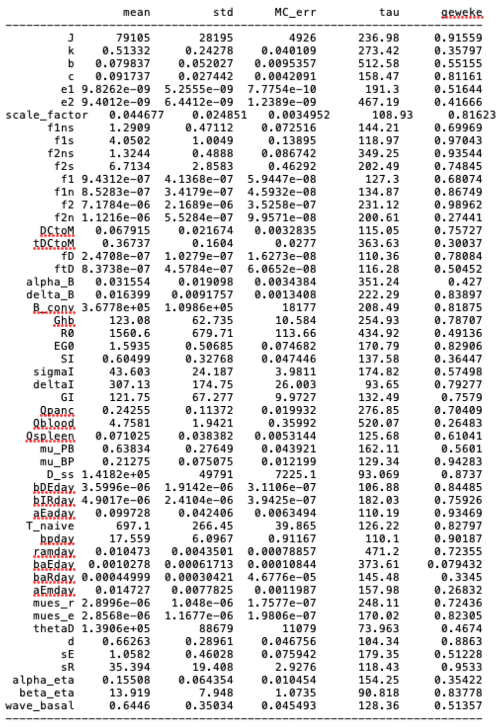
```
                  mean         std      MC_err         tau      geweke
----------------------------------------------------------------------
          J      44416       20882      2278.7      68.346     0.49525
          k    0.31234     0.20523    0.036059      146.14     0.37978
          b    0.10093    0.057858     0.01011      240.54     0.14883
          c    0.10904    0.038945   0.0063701      353.26     0.65924
         e1 1.0133e-08  5.0686e-09  7.2235e-10      136.67     0.96843
         e2 1.2032e-08  3.4627e-09   5.937e-10       444.1     0.82188
scale_factor   0.061873    0.037462   0.0045067      101.93     0.92154
       f1ns    0.89546     0.39421     0.04386      79.683     0.84238
        f1s       2.53     0.81444     0.13853       314.1     0.63338
       f2ns     1.0983     0.47046    0.068344      115.31     0.97182
        f2s     5.0609      2.6989     0.43879      128.74     0.36715
         f1 1.8055e-06  8.1474e-07  1.0916e-07      105.81      0.5451
        f1n 6.5163e-07   3.549e-07  5.0729e-08      129.88     0.90574
         f2  3.237e-06  1.4933e-06  2.2003e-07      425.88     0.81732
        f2n 6.2916e-07  3.2402e-07  4.0703e-08      109.92      0.9149
      DCtoM   0.051934     0.02734   0.0031485      87.637     0.65319
     tDCtoM    0.36128     0.14515    0.023961       137.4     0.69181
         fD 1.7844e-07  8.8134e-08  1.1609e-08       100.8     0.56976
        ftD 9.4642e-07  3.8735e-07  5.5659e-08      129.93     0.85292
    alpha_B   0.029858    0.011126   0.0015704      388.54      0.6157
    delta_B   0.016316   0.0069814  0.00091447      182.62     0.53902
     B_conv 2.3109e+05  1.5455e+05       18424      112.54     0.64197
        Ghb     106.31      45.163       7.563      346.79     0.95247
         R0     906.34      385.44       65.14      526.32     0.47042
        EG0     1.6875      0.5386     0.10083       459.5     0.62726
         SI    0.72627     0.33426    0.048765      281.21     0.29541
     sigmaI     39.107      20.092      3.6654      557.48     0.66956
     deltaI     381.06       196.5       25.63      84.664      0.5493
         GI     161.43       68.88      8.6529      111.44     0.77853
      Qpanc    0.21378     0.12537    0.021765         144     0.16811
     Qblood     2.7913      1.3291     0.15739      84.195     0.95495
    Qspleen     0.1257    0.032759   0.0054556      198.91     0.89295
      mu_PB    0.50404     0.25871    0.029535      72.388      0.9798
      mu_BP    0.11267    0.044521   0.0062249      145.58     0.68107
       D_ss 1.0776e+05       66387       11090      136.45     0.26052
     bDEday 4.4993e-06  2.5317e-06  3.1119e-07      94.873      0.4493
     bIRday  7.209e-06  3.2981e-06  4.3692e-07         109     0.98611
     aEaday    0.15501    0.056041   0.0092456      229.27     0.58145
    T_naive     413.82      143.39      14.727      68.096     0.75815
      bpday     13.159      5.5801     0.85945      252.33     0.74494
     ramday  0.0094069   0.0038764  0.00045029      92.559     0.86816
     baEday 0.00093258  0.00052548  7.4912e-05      104.42     0.47109
     baRday 0.00071333  0.00052042  7.9434e-05      210.67     0.71858
     aEmday   0.011719   0.0033175  0.00049001      129.29      0.8265
     mues_r 1.9124e-06  1.0162e-06  1.2536e-07       115.1     0.96604
     mues_e 2.4218e-06  9.7888e-07  1.4066e-07      103.22     0.90941
     thetaD 1.7636e+05  1.0313e+05       13688      135.98     0.52317
          d    0.58828     0.21802    0.031293      100.23     0.88965
         sE    0.69003     0.43578    0.054855      91.307     0.47922
         sR     40.589      18.868       2.673      167.81     0.29673
  alpha_eta    0.15817    0.043207   0.0067333      158.07     0.81184
   beta_eta     19.605      9.4936      1.3923      136.48     0.72054
 wave_basal     1.1036     0.41974     0.06363      216.31     0.65559
----------------------------------------------------------------------
```

(b) Table showing mean parameter values and convergence criteria Geweke. We consider Geweke > 0.7 to have converged.

Figure 14: Results of DRAM on NOD mouse + wave + acute mouse data.



(a) Parameter density plots



```
                   mean          std       MC_err         tau      geweke
-------------------------------------------------------------------------
          J       79105        28195         4926      236.98     0.91559
          k     0.51332      0.24278     0.040109      273.42     0.35797
          b    0.079837     0.052027    0.0095357      512.58     0.55155
          c    0.091737     0.027442    0.0042091      158.47     0.81161
         e1  9.8262e-09   5.2555e-09   7.7754e-10       191.3     0.51644
         e2  9.4012e-09   6.4412e-09   1.2389e-09      467.19     0.41666
scale_factor    0.044677     0.024851    0.0034952      108.93     0.81623
       f1ns      1.2909      0.47112     0.072516      144.21     0.69969
        f1s      4.0502       1.0049      0.13895      118.97     0.97043
       f2ns      1.3244       0.4888     0.086742      349.25     0.93544
        f2s      6.7134       2.8583      0.46292      202.49     0.74845
         f1  9.4312e-07   4.1368e-07   5.9447e-08       127.3     0.68074
        f1n  8.5283e-07   3.4179e-07   4.5932e-08      134.87     0.86749
         f2  7.1784e-06   2.1689e-06   3.5258e-07      231.12     0.98962
        f2n  1.1216e-06   5.5284e-07   9.9571e-08      200.61     0.27441
      DCtoM    0.067915     0.021674    0.0032835      115.05     0.75727
     tDCtoM     0.36737       0.1604       0.0277      363.63     0.30037
         fD  2.4708e-07   1.0279e-07   1.6273e-08      110.36     0.78084
        ftD  8.3738e-07   4.5784e-07   6.0652e-08      116.28     0.50452
    alpha_B    0.031554     0.019098    0.0034384      351.24       0.427
    delta_B    0.016399    0.0091757    0.0013408      222.29     0.83897
     B_conv  3.6778e+05   1.0986e+05        18177      208.49     0.81875
        Ghb      123.08       62.735       10.584      254.93     0.78707
         R0      1560.6       679.71       113.66      434.92     0.49136
        EG0      1.5935      0.50685     0.074682      170.79     0.82906
         SI     0.60499      0.32768     0.047446      137.58     0.36447
     sigmaI      43.603       24.187       3.9811      174.82     0.57498
     deltaI      307.13       174.75       26.003       93.65     0.79277
         GI      121.75       67.277       9.9727      132.49      0.7579
      Qpanc     0.24255      0.11372     0.019932      276.85     0.70409
     Qblood      4.7581       1.9421      0.35992      520.07     0.26483
    Qspleen    0.071025     0.038382    0.0053144      125.68     0.61041
      mu_PB     0.63834      0.27649     0.043921      162.11      0.5601
      mu_BP     0.21275     0.075075     0.012199      129.34     0.94283
       D_ss  1.4182e+05        49791       7225.1      93.069      0.8737
     bDEday  3.5996e-06   1.9142e-06   3.1106e-07      106.88     0.84485
     bIRday  4.9017e-06   2.4104e-06   3.9425e-07      182.03     0.75926
     aEaday    0.099728     0.042406    0.0063494      110.19     0.93469
    T_naive       697.1       266.45       39.865      126.22     0.82797
      bpday      17.559       6.0967      0.91167       110.1     0.90187
     ramday    0.010473    0.0043501   0.00078857       471.2     0.72355
     baEday   0.0010278   0.00061713   0.00010844      373.61    0.079432
     baRday  0.00044999   0.00030421   4.6776e-05      145.48      0.3345
     aEmday    0.014727    0.0077825    0.0011987      157.98     0.26832
     mues_r  2.8996e-06    1.048e-06   1.7577e-07      248.11     0.72436
     mues_e  2.8568e-06   1.1677e-06   1.9806e-07      170.02     0.82305
     thetaD  1.3906e+05        88679        11079      73.963      0.4674
          d     0.66263      0.28961     0.046756      104.34      0.8863
         sE      1.0582      0.46028     0.075942      179.35     0.51228
         sR      35.394       19.408       2.9276      118.43      0.9533
  alpha_eta     0.15508     0.064354     0.010454      154.25     0.35422
   beta_eta      13.919        7.948       1.0735      90.818     0.83778
 wave_basal      0.6446      0.35034     0.045493      128.36     0.51357
-------------------------------------------------------------------------
```

(b) Table showing mean parameter values and convergence criteria Geweke. We consider Geweke > 0.7 to have converged.

Figure 15: Results of DRAM on NOD mouse + wave + progressive mouse data.