



Clinical Data for Advanced Glucose Modeling

Duun-Henriksen, Anne Katrine; Schmidt, Signe; Nøgaard, Kirsten; Madsen, Henrik

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Duun-Henriksen, A. K., Schmidt, S., Nøgaard, K., & Madsen, H. (2013). *Clinical Data for Advanced Glucose Modeling*. Technical University of Denmark. DTU Compute Technical Report-2013 No. 06

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Clinical Data for Advanced Glucose Modeling

Anne Katrine Duun-Henriksen^{a,*}, Signe Schmidt^b, Kirsten Nøgaard^b, Henrik Madsen^a

^a Department of Applied Mathematics and Computer Science, Technical University of Denmark

^b Department of Endocrinology, Hvidovre University Hospital

Abstract

Keywords: Type 1 diabetes, Blood glucose modelling, PK-PD modelling, Experimental design

1 Introduction

This report is a supplement to a data set from a clinical study performed at Hvidovre University Hospital, Denmark as a part of the DIACON (Diabetes in Control) project in 2009-2010. The DIACON project is an interdisciplinary team situated in Denmark with both clinicians and scientist involved in the project. The aim of the DIACON project is to develop automatic treatment methods for type 1 diabetes and thereby improve the quality of life for the patients. The ultimate goal is to obtain fully closed loop control of the blood glucose level. This is known as the artificial pancreas and consists of continuous subcutaneous insulin infusion (CSII) from a pump, a continuous glucose monitor (CGM) obtaining the blood glucose level and finally, a control algorithm regulating the insulin pump based on feed back from the CGM. The controller determines the optimal amount of insulin to keep the blood glucose in the target range. An illustration of the components of an artificial pancreas is seen in Figure 1.

In the development of control algorithms for an artificial pancreas, virtual type 1 diabetes patients are a useful tool for pre-clinical testing and verification. The advantages are several: acceleration of the development process, lower costs, and the possibility of testing extreme treatment strategies without having to deal with the ethical aspects.

One of the purposes of the DIACON project is to develop a robust and reliable model of the insulin-blood glucose dynamical system. To be able to do this we needed a data set including observations of the system in type 1 diabetes patients.

Since the insulin-blood glucose system is a very complex system affected by many different factors such as meals, physical exercise and changes in stress level etc., the study had to be quite controlled. Further, a previous ambulant study had shown that out clinic data is too noise corrupted and unreliable due

* *Contact author:*

Technical University of Denmark
Department of Applied Mathematics and Computer Science
Matematiktorvet, Building 322, DK-2800 Kgs. Lyngby, Denmark
Tel: +45 4525 3399, email: akdu@dtu.dk

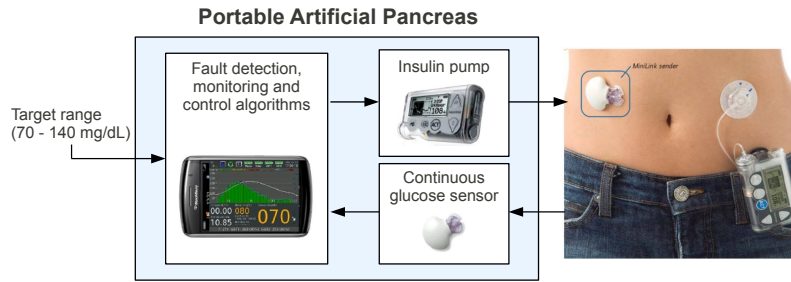


Figure 1: *Illustration of the artificial pancreas.*

to unknown disturbances and incorrect reportings by the involved patients. For these reasons the data collection was performed in clinic and designed to mirror the every day life of type 1 diabetes patients.

Meals, insulin boluses, and physical exercise were included as factors (controlled inputs) since they are believed to have the greatest effect on the blood glucose level. By separating the occurrence of the factors and initiating them in changing order a total of 24 different sequences were constructed. The obtained data set is extensive and hence useful for many different modeling purposes.

The present report can be seen as an introduction to the study design and a guide to the data files including all data. It is intended for students, researchers or clinicians who wish to use the data for modeling purposes or get insight into the insulin-blood glucose dynamics.

Furthermore, the majority of the results of this study has been published in the paper "Effects of Everyday Life Events on Glucose, Insulin, and Glucagon Dynamics in Continuous Subcutaneous Insulin Infusion-Treated Type 1 Diabetes: Collection of Clinical Data for Glucose Modeling" in the journal "Diabetes Technology and Therapeutics", see [2] for details.

The following sections will explain the study design in detail including subject statistics followed by a presentation of all the data observed and a guide to the data files following this report.

2 Description of the study design

As mentioned in the introduction, to collect data suitable for advanced modelling of type 1 diabetes is advantageous to do a controlled in-clinic study to avoid disturbances by uncontrolled factors. This section describes the study design.

2.1 Study design

The clinical study was designed from the theory of classical design of experiments. The basis was a factorial design with three main factors, each investigated on two levels. The factors and the defined levels are described in detail in section 2.2. The study consisted of 24 different sequences (study days) in which the three factors were combined differently.

In every day life the factors affecting the blood glucose level are often confounded, e.g., a meal is usually accompanied by an insulin bolus. Hence it can be difficult to estimate the true effect of each factor. To avoid problems with unidentifiability due to confounding factors, the occurrence of the events was separated in time by 150 minutes. A study day included three different events in total.

The combination and order of event types is seen in Figure 2. The first event was always a meal since the patients had been fasting for at least 10 hours before start. The second and third event was either

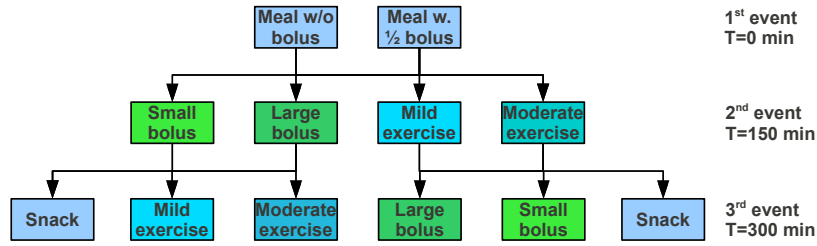


Figure 2: Schematic overview of the study design. In total the study included 24 different sequences. T is study time.

a bolus, exercise or a snack. Prior to the first event was a stabilization period from 8AM to 10AM ($T=0$ min) to bring the blood glucose level in the normal range. Likewise, was the last event ($T=300$ min) followed by a stabilization period to make the patient ready to leave the clinic.

2.2 Event types

In this study the three events investigated was: Meal including fast-acting carbohydrates, exercise on a treadmill and insulin boluses. Each event type was studied at two levels. Additionally, some study days included a liquid snack. A description of the levels is seen in table 1.

The meal was either given with half the meal bolus or with no bolus at all. The size of the meal bolus was determined from the subjects weight and personal insulin-to-carbohydrate ratio (ICR). ICR is defined as the amount of carbohydrate in milligrams one unit of insulin can counterbalance. The energy composition of the meal was 52% carbohydrates, 18%protein and 30% fat. It included simple carbohydrates form white bread, ham, cheese, margarine, marmalade, milk and juice. The snack was a protein drink with an energy composition of 89% carbohydrates and 11% protein. The size of the meal and snack was determined from the body weight as seen in Table 1.

Exercise was separated in a mild and moderate level, the former defined as 50% of interval between resting heart rate and maximum heart rate and the latter as 75%. An insulin bolus was separated into a small and large bolus, a small bolus was defined to lower blood glucose by 3 mmol/L based on the personal insulin sensitivity factor (ISF) and a large bolus was defined to lower blood glucose by 6 mmol/L based on personal ISF. ISF is defined as point drop in plasma glucose (mmol/L) per unit of insulin.

Table 1: Description of event types

Event type	Levels	Description
Meal	Unbolused	Solid food with drink. 1 g of CHO/kg body weight. No meal bolus.
	Underbolused	Solid food with drink. 1 g of CHO/kg body weight. 50% of the insulin bolus matching the meal CHO content based on personal ICR.
Exercise	Mild	$0.5 \times (\text{maximum HR} - \text{resting HR}) + \text{resting HR}$.
	Moderate	$0.7 \times (\text{maximum HR} - \text{resting HR}) + \text{resting HR}$.
Bolus	Small	Insulin bolus estimated to lower blood glucose level by 3 mmol/L based on personal ISF.
	Large	Insulin bolus estimated to lower blood glucose level by 6 mmol/L based on personal ISF.
Snack	NA	Liquid. 0.4 g of CHO/kg of body weight.

2.3 Data collection

During the study day blood glucose level was analyzed every ten minutes. Insulin level was analyzed every ten minutes 30 minutes after an event otherwise every 30 minutes. Additionally, glucagon, cortisol, growth hormone, and epinephrine and norepinephrine levels were analyzed according to the same scheme as insulin. The CGM recorded the sensor glucose level every 5 minutes. The Actiheart recorded activity and heart rate every minute.

3 Description of patients and equipment

This section present physiological details about the patients and details regarding the equipment used for monitoring and analysis.

3.1 Patients

Twelve type 1 diabetes patients participated in the study. They were all recruited from the diabetes clinic at Hvidovre Hospital. All were treated with insulin aspart (Novo Nordisk, Bagsv rd, Denmark) using a pump (Paradigm 522/722 from Medtronic, Northridge, CA) for at least six months before the first visit. The patient characteristics are shown in table 2.

Table 2: *Patient Characteristics*

Female sex	75%
Age	34.3±9.1 years
Body mass index	25.1±4.3 kg/m ²
Diabetes duration	16.5±10.2 years
C-peptide	0.097±0.078 nmol/L
Hemoglobin A1c	6.7±0.4%
Total daily insulin	0.63±0.11 U/kg/day

3.2 Equipment for blood analysis

The blood samples drawn during the study where analyzed for different hormone concentrations and blood glucose concentration. This section describes the methods and equipment used for these analysis.

Blood glucose was analyzed with gold standard equipment (YSI2300 STAT Plus, Yellow Springs Instruments, Yellow Springs, OH).

Insulin aspart was analyzed with a specific immunoassay using the LOCI-technology at Novo Nordisk A/S, M l v, Denmark.

The glucagon analysis was made with a pancreas specific glucagon assay with a low detection limit at the Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. The glucagon assay was directed against the C-terminal of the glucagon molecule (antibody code no. 4305) and therefore measures glucagon of mainly pancreatic origin

Cortisol was analyzed with Solid-phase chemiluminiscense competitiv immunometric assay and growth hormone was analyzed with Solid-phase two-site chemiluminiscense immunometric assay both on Immulite 2000 (Siemens Healthcare Diagnostics) at Department of clinical biochemistry, Hvidovre Hospital, Denmark.

For the plasma catecholamine extraction procedure the The concentration of epinephrine and norepinephrine was determined by HPLC with electrochemical detection (Pcat extraction kit part no: 45-0141,

Thermo Fisher Scientific, California, USA). The column was a Prodigy 3u ODS (3) C18 (2 mm x 100 mm, particle size 3 μm , phenomenex). The mobile phase consisted of 55 mM sodium acetate, 1 mM octanesulfonic acid, 0.1 mM Na₂EDTA and 8% Acetonitrile, adjusted to pH 3.2 with 0.1M acetic acid, and was degassed using an on-line degasser. Twenty μl of the samples were injected and the flow rate was 0.15 mL/min. The electrochemical detection was accomplished using an amperometric detector (Antec Decade from Antec, Leiden, The Netherlands) with a glassy carbon electrode set at 0.8 V, with an Ag/AgCl as reference electrode.

3.3 Activity monitor and continuous glucose monitor

To monitor the activity level of the patients, the Actiheart (CamNtech Ltd., Cambridge,UK) was used. The Actiheart monitors heart rate and activity from an accelerometer. During the study the patients also wore a CGM (Paradigm Real-Time, Medtronic) observing the glucose level in the subcutaneous layer.

4 Description of data files

For each study day a .csv file with all the data exists. All types of outputs and covariates are included. The time resolution is in minutes. Furthermore, an info file and comments file are included for each sequence.

Some of the data files includes missing observations. Look in the comments file for information about missing observations and other discrepancies between the planned sequence and what was performed.

In the table below all the input and outputs are stated in the order they appear in the data file. First column is a time vector which is followed by four inputs vectors corresponding to carbohydrates, insulin delivery, IV glucose administration and prescribed exercise level determined from the beats per minute (BPM). Hereafter blood glucose (YSI) and sensor glucose (CGM) values are stated followed by insulin plasma concentration and the remaining hormones stated in section 2.3. Finally, data and information from the Actiheart are listed.

The content of the info file can be seen in table 4. It contains information about the study: date, and sequence no., and information about the patient, e.g., age, weight, resting heart rate (HR), and basal insulin rate settings for the pump.

The comments files include a time vector corresponding to the one in the data files and the comments from the physician in charge of the study. They also include blood pressure observations obtained during the study day.

The data files are named with a number representing the participant and the letter 'a' or 'b' indicating whether it is the first or the second study day for that participant. E.i. the data file for participant no. 3's second event is named 03b_data.csv. The info and comments files are named 03b_info.csv and 03b_comments.csv respectively.

4.1 Conversion of units

In glucose modelling and diabetes research, different units are used for blood glucose and sensor glucose level. The most often used unit for insulin is units. In table 5 is the different conversion factors for glucose and insulin stated. For the plots presented later in this report, the unit for cortisol was changed from nmol/L to ng/mL. This conversion is also included in the table.

Table 3: *Data file content*

Variable	Unit	Description
TT	[min]	Trial time
CHO	[g]	Carbohydrate intake
I_{in}	[U]	Insulin delivery from the pump
G_{in}	[g]	I.V. Glucose delivery
EX	[BPM]	Prescribed exercise level
YSI	[mmol/L]	Plasma glucose level
CGM	[mmol/L]	Subcutaneous glucose level
I_{out}	[pM]	Insulin concentration in plasma
GG	[pM]	Glucagon concentration in plasma
CS	[nmol/L]	Cortisol concentration in plasma
GH	[ng/mL]	Growth hormone concentration in plasma
AL	[ng/mL]	Adrenaline concentration in plasma
NL	[ng/mL]	Noradrenaline concentration in plasma
ACT	[Counts]	Activity level
CL_BPM	[BPM]	Observed heart rate (cleaned)
Raw_BPM	[BPM]	Observed heart rate (raw)
OK/Rec	[-]	Index indicating whether the BPM recording is properly recorded (OK) or had to be recovered (Rec)
ECG (μV)	[μV]	Eccardiogram observations used to calculate ACT
Lt s	[s]	Amount of lots seconds in the current minute in the Actiheart
J/ep	[Joule]	Joules per epoch
J/ep/kg	[Joule]	Joules per epoch per kilo body weight

5 Plots of data

This section presents plots of the entire data set. In Table 6 an overview of the entire study is presented.

Each plot presents the specific sequence and timing and size of inputs: Meals, insulin boluses and intravenously administrated glucose. Furthermore, all the analyzed observations are plotted, e.g., YSI, CGM, Insulin aspart, glucagon, heart rate, activity, norepinephrine, epinephrine, cortisol and growth hormone. The title of the plots is participant no. and a or b referring to the first or second study day for that participant. Note that for participant no. 01 they are named 01b and 01c since we performed a pilot study on this participant which is not included. Participant no. 9 was excluded from the study due to pregnancy and no data exists from this participant. An additional participant was included instead (no. 13).

Table 4: *Info file content*

Variable	Description
Date	Date of the study day
Sequence no.	1:24
Patient ID	Initials and date of birth
Patient trial no.	States the patients no. of visit.
Age	Age in years
Sex	M/F
Weight	Body weight in kg
Height	Height in meters
Norm. ICR	The patient's normal insulin-to-carbohydrate ratio
Norm. ISF	The patient's normal insulin sensitivity factor
Basal insulin rate	Time interval: Basal rate
Target BG	The target blood glucose
Resting HR	Resting heart rate
Maximum HR	Maximum heart rate
Actiheart	Device A or B
Sensor placement	States the placement of the sensor on the body
Pump placement	States the placement of the pump on the body
Diabetes debut	Year of diabetes debut
Medication	List of the patient's medication (if any)

Table 5: *Conversion of units*

Glucose [1]	1 mmol/L	18.0182 mg/dL
Insulin[1]	6 pM	1 mU/L
Cortisol [1]	1 nmol/L	2.759 ng/mL

Table 6: Overview of the clinical DIACON study 2009-2010

Patient #	Event 1	Event 2	Event 3	Short code
01.b	Meal w/o bolus	Moderate exercise	Large bolus	0bMOeLb
01.c	Meal w $\frac{1}{2}$ bolus	Moderate exercise	Small bolus	$\frac{1}{2}$ bMOeSb
02.a	Meal w $\frac{1}{2}$ bolus	Small bolus	Mild exercise	$\frac{1}{2}$ bSbMIe
02.b	Meal w $\frac{1}{2}$ bolus	Mild exercise	Small bolus	$\frac{1}{2}$ bMIeSb
03.a	Meal w/o bolus	Large bolus	Mild exercise	0bLbMIe
03.b	Meal w $\frac{1}{2}$ bolus	Large bolus	Moderate exercise	$\frac{1}{2}$ bLbMOe
04.a	Meal w $\frac{1}{2}$ bolus	Small bolus	Snack	$\frac{1}{2}$ bSbSn
04.b	Meal w $\frac{1}{2}$ bolus	Mild exercise	Large bolus	$\frac{1}{2}$ bMIeLb
05.a	Meal w $\frac{1}{2}$ bolus	Moderate exercise	Snack	$\frac{1}{2}$ bMOeSn
05.b	Meal w/o bolus	Small bolus	Snack	0bSbSn
06.a	Meal w $\frac{1}{2}$ bolus	Large bolus	Mild exercise	$\frac{1}{2}$ bLbMIe
06.b	Meal w $\frac{1}{2}$ bolus	Moderate exercise	Large bolus	$\frac{1}{2}$ bMOeLb
07.a	Meal w/o bolus	Mild exercise	Small bolus	0bMIeSb
07.b	Meal w/o bolus	Moderate exercise	Small bolus	0bMOeSb
08.a	Meal w/o bolus	Mild exercise	Snack	0bMIeSn
08.b	Meal w/o bolus	Large bolus	Moderate exercise	0bLbMOe
10.a	Meal w $\frac{1}{2}$ bolus	Moderate exercise	Small bolus	$\frac{1}{2}$ bMOeSb
10.b	Meal w $\frac{1}{2}$ bolus	Mild exercise	Snack	$\frac{1}{2}$ bMIeSn
11.a	Meal w $\frac{1}{2}$ bolus	Large bolus	Snack	$\frac{1}{2}$ bLbSn
11.b	Meal w/o bolus	Mild exercise	Large bolus	0bMIeLb
12.a	Meal w/o bolus	Small bolus	Moderate exercise	0bSbMOe
12.b	Meal w/o bolus	Moderate exercise	Snack	0bMOeSn
13.a	Meal w/o bolus	Small bolus	Mild exercise	0bSbMIe
13.b	Meal w/o bolus	Large bolus	Snack	0bLbSn

The code in the last column is combined of the three event during the study day. 0b corresponds to a meal w/o bolus and $\frac{1}{2}$ b corresponds to a meal w/ half bolus. Lb corresponds to at large bolus. Sb corresponds to a small bolus. MOe corresponds to moderate exercise. MIe corresponds to mild exercise. Sn corresponds to a snack.

Trial no. 01b

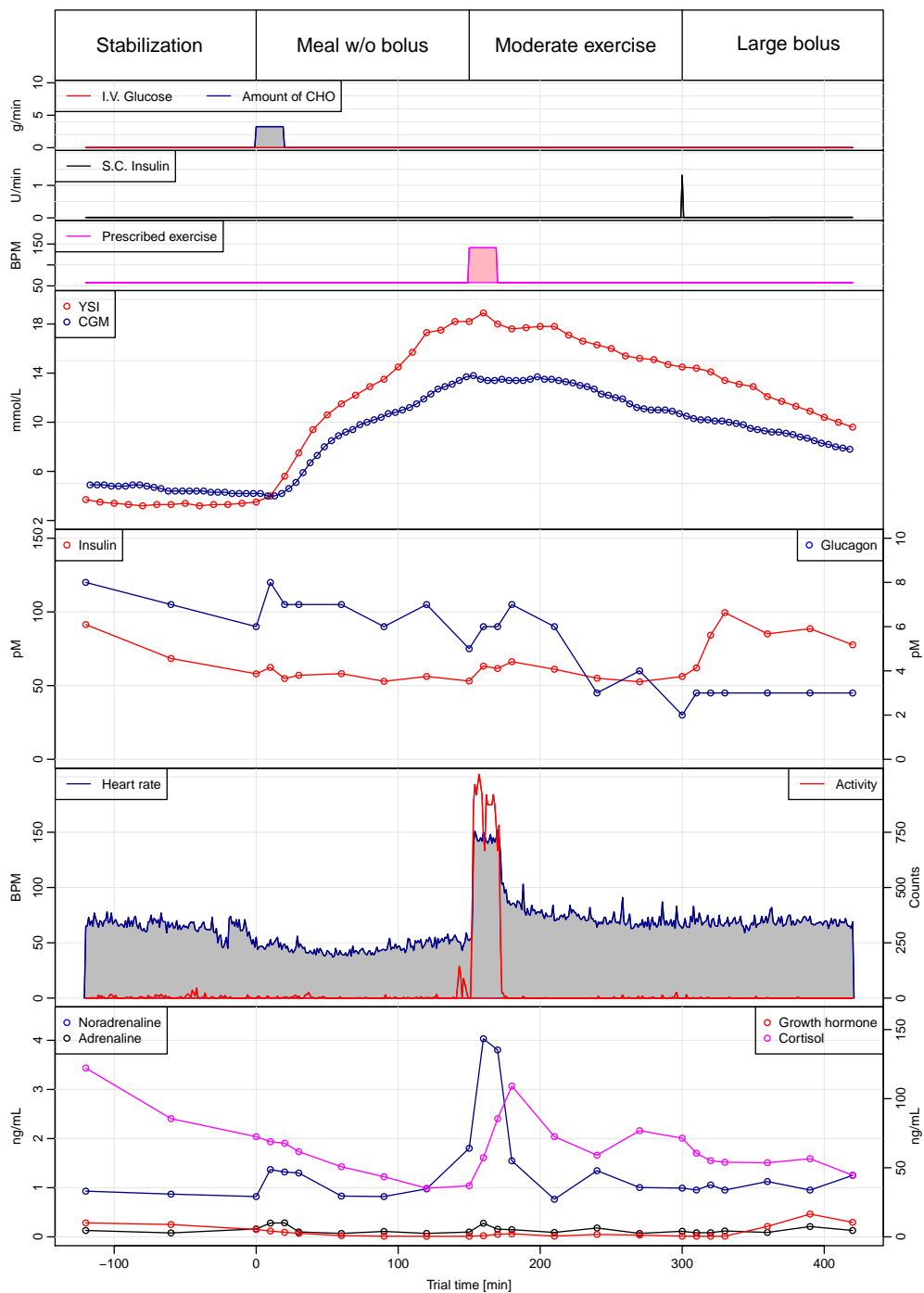


Figure 3: Results from trial 01b. Note that the S.C. insulin is above zero according to table II at all times even though it is hard to see.

Trial no. 01c

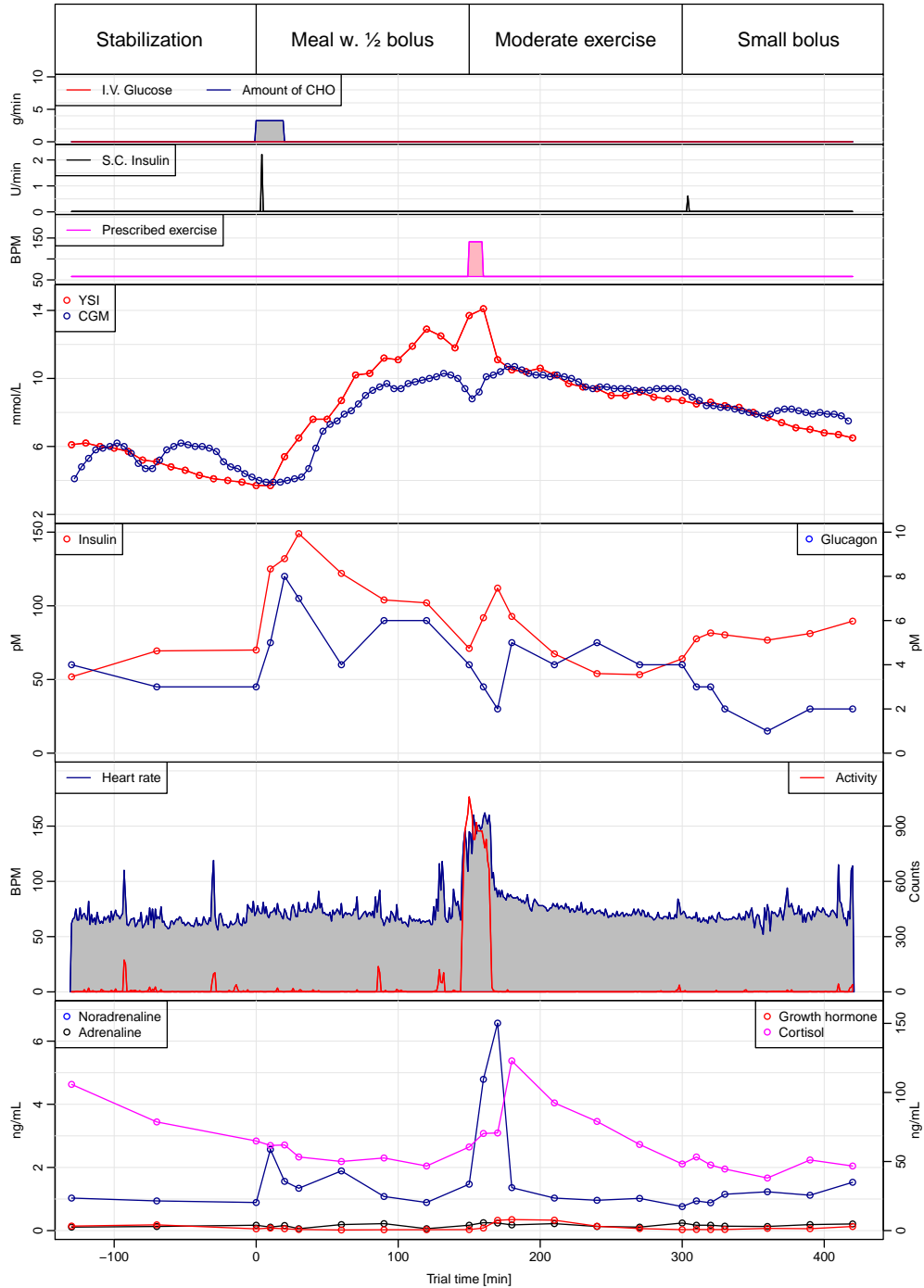


Figure 4: Results from trial 01c. Note that the S.C. insulin is above zero according to the info file.

Trial no. 02a

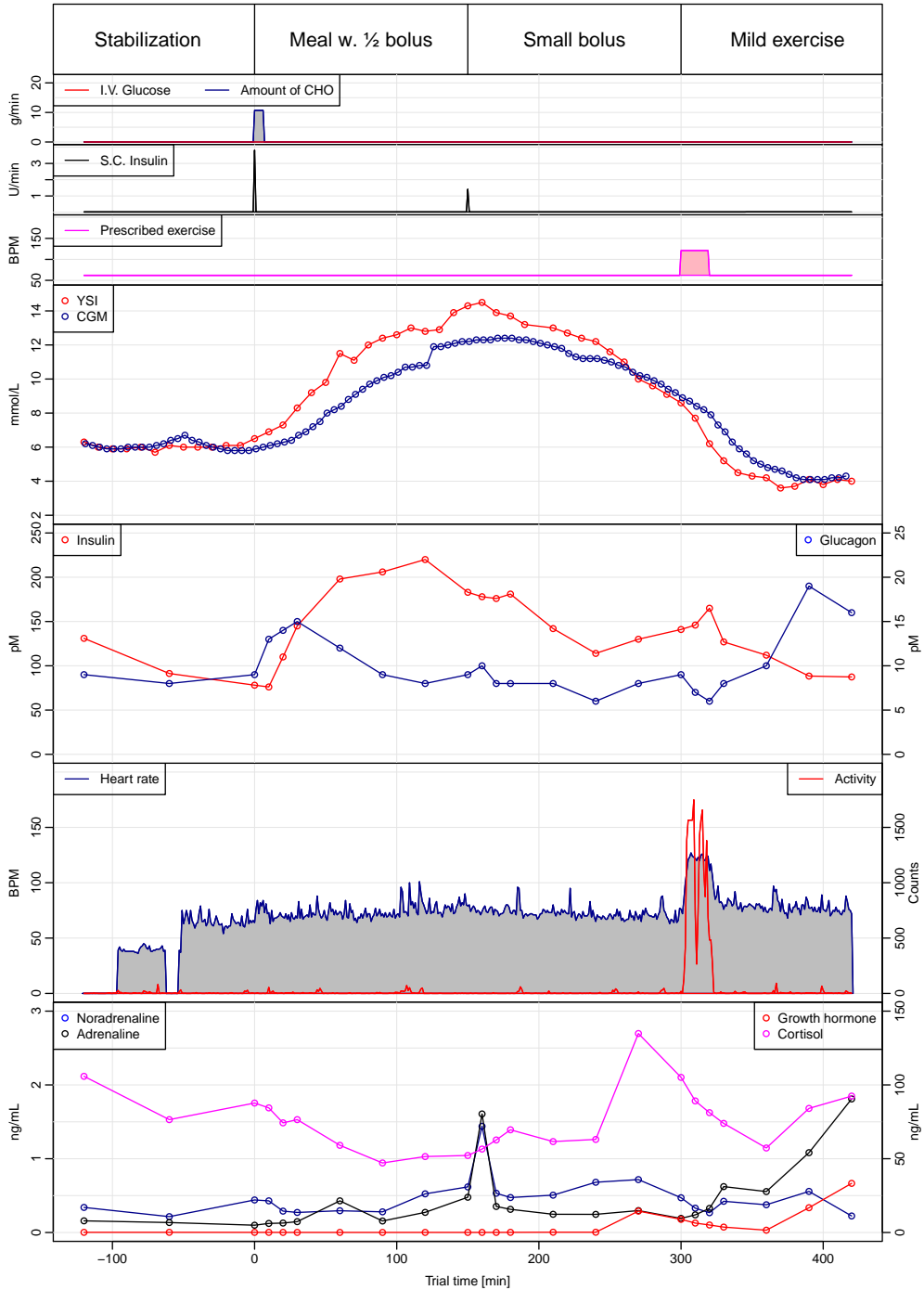


Figure 5: Results from trial 02a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 02b

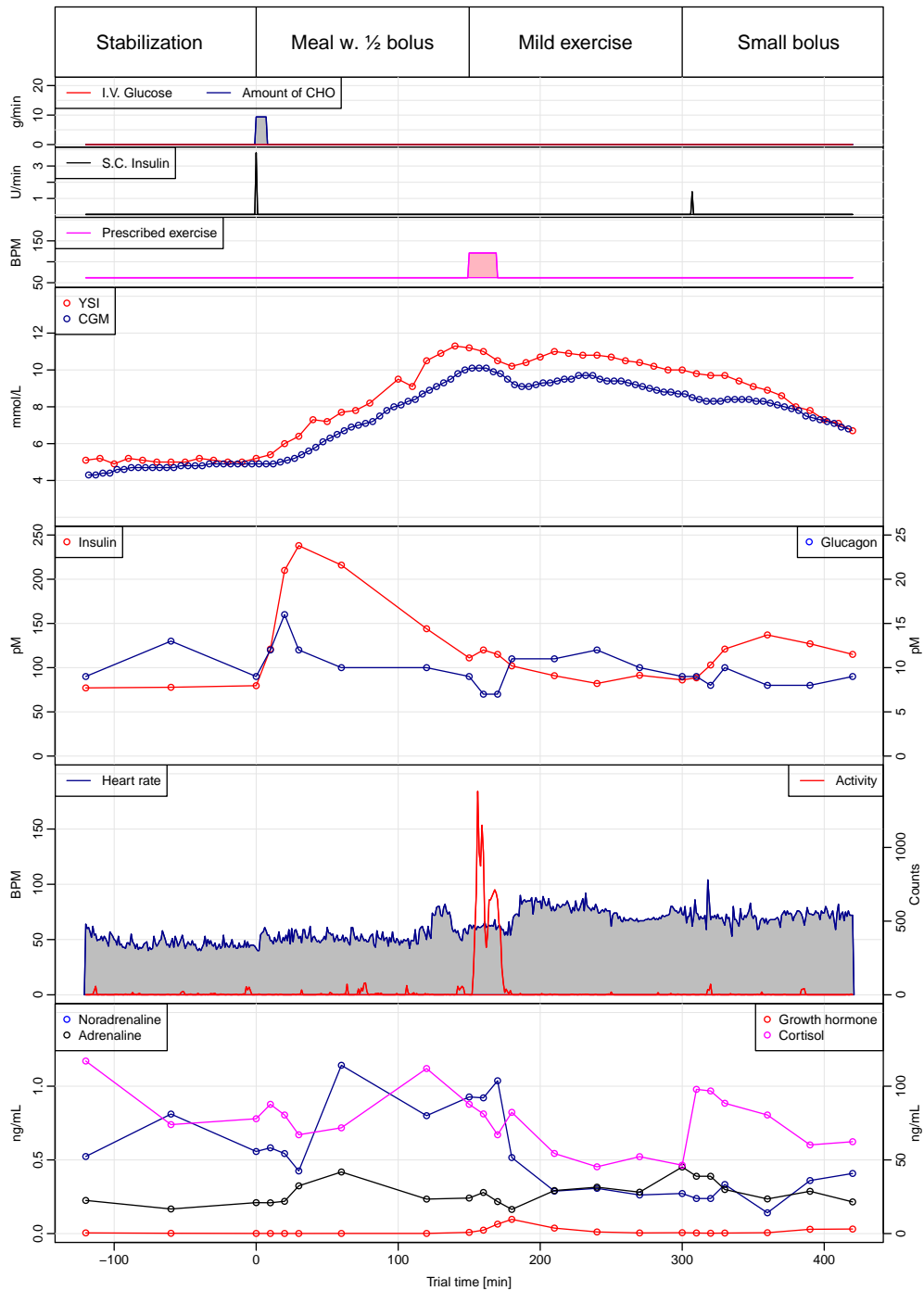


Figure 6: Results from trial 02b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 03a

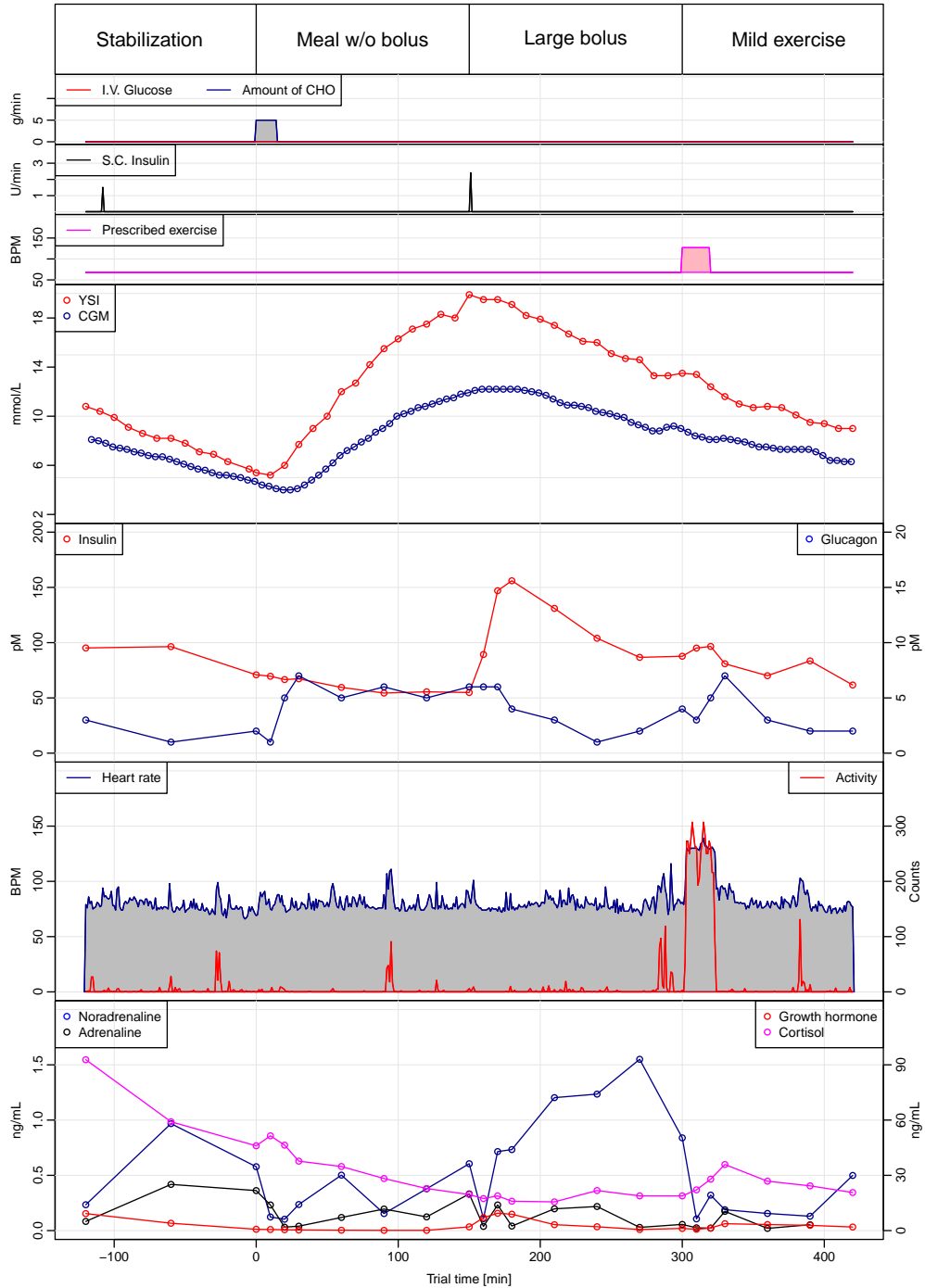


Figure 7: Results from trial 03a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 03b

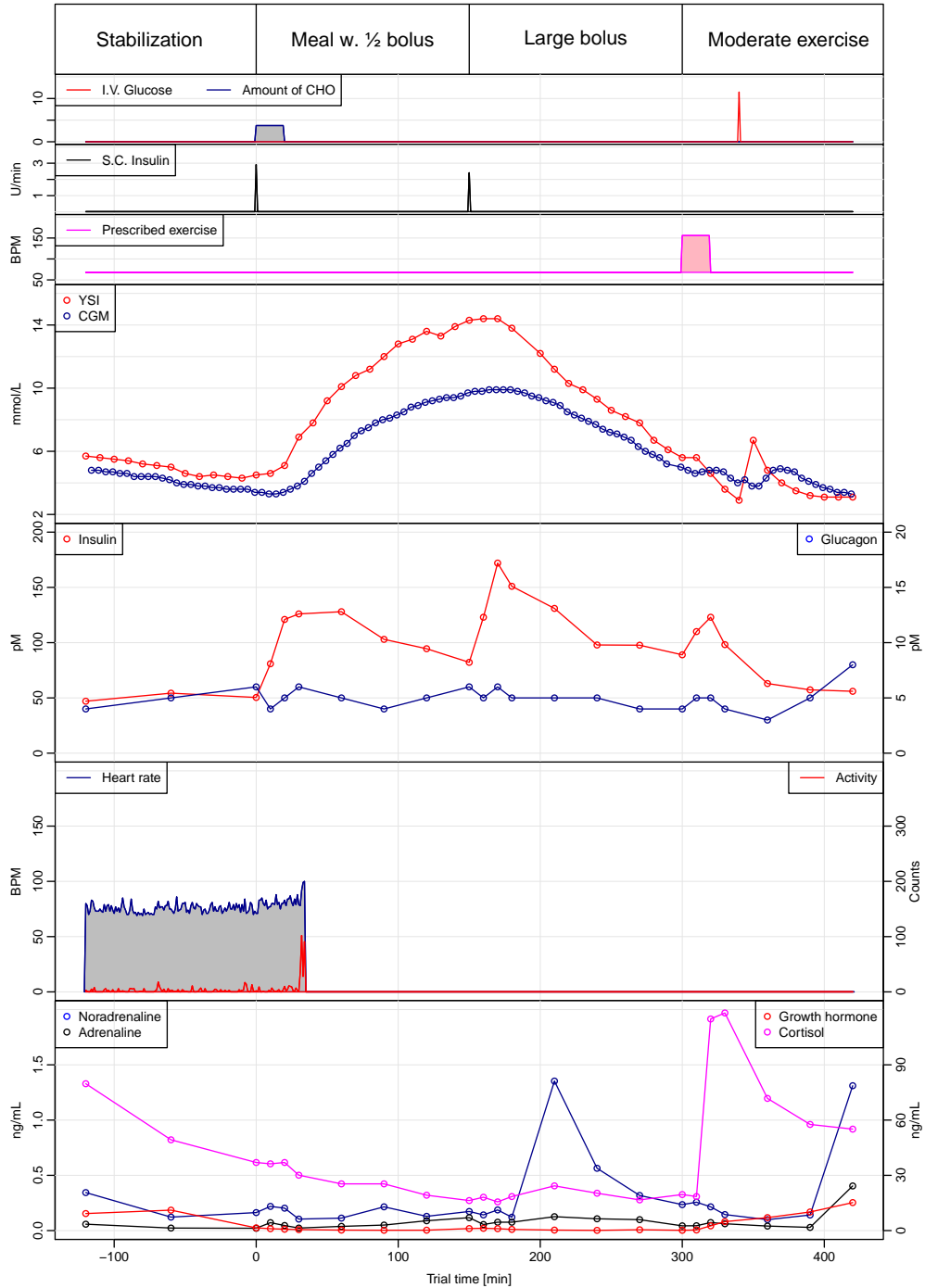


Figure 8: Results from trial 03b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 04a

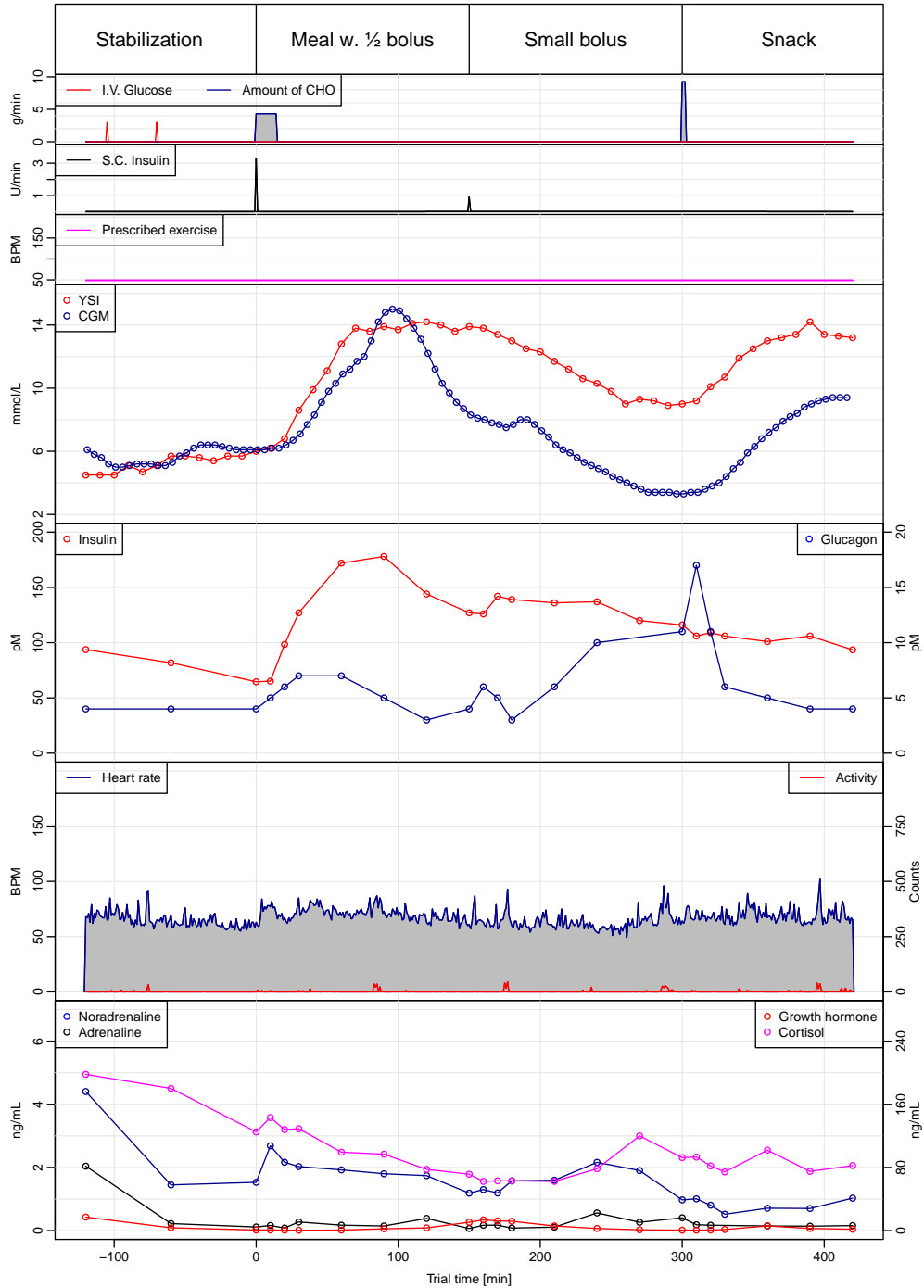


Figure 9: Results from trial 04a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 04b

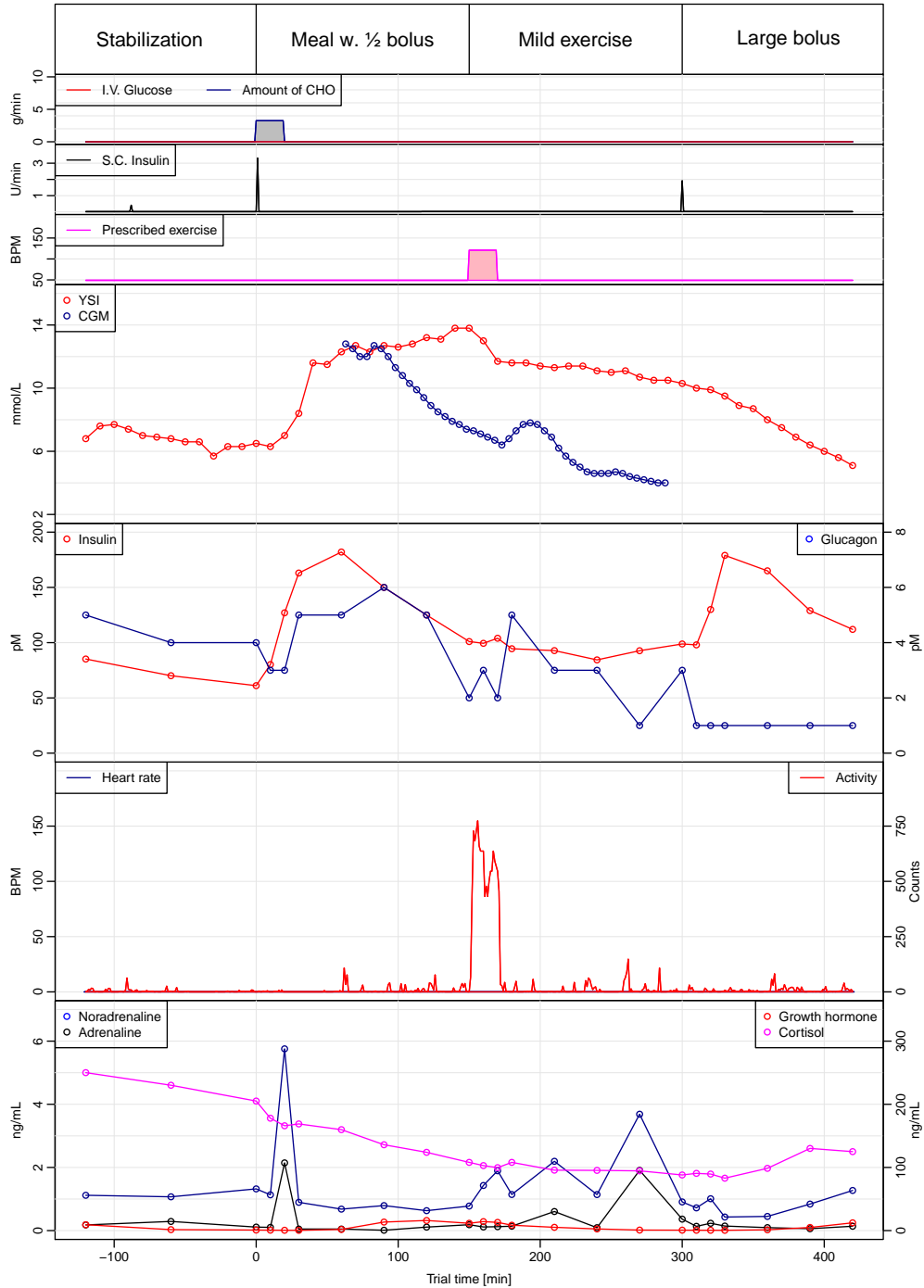


Figure 10: Results from trial 04b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 05a

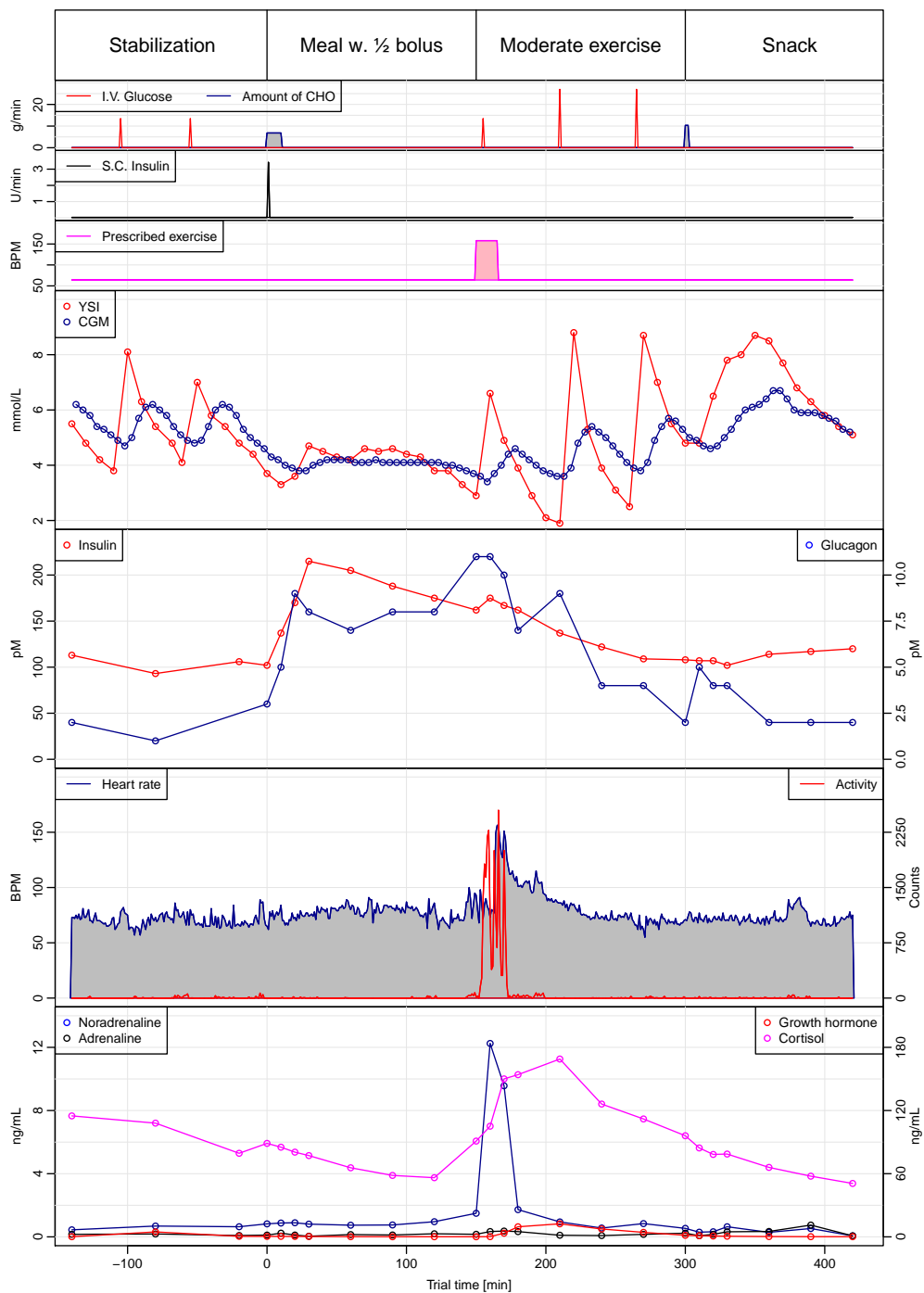


Figure 11: Results from trial 05a. Note that the S.C. insulin is above zero according to table II at all times even though it is hard to see.

Trial no. 05b

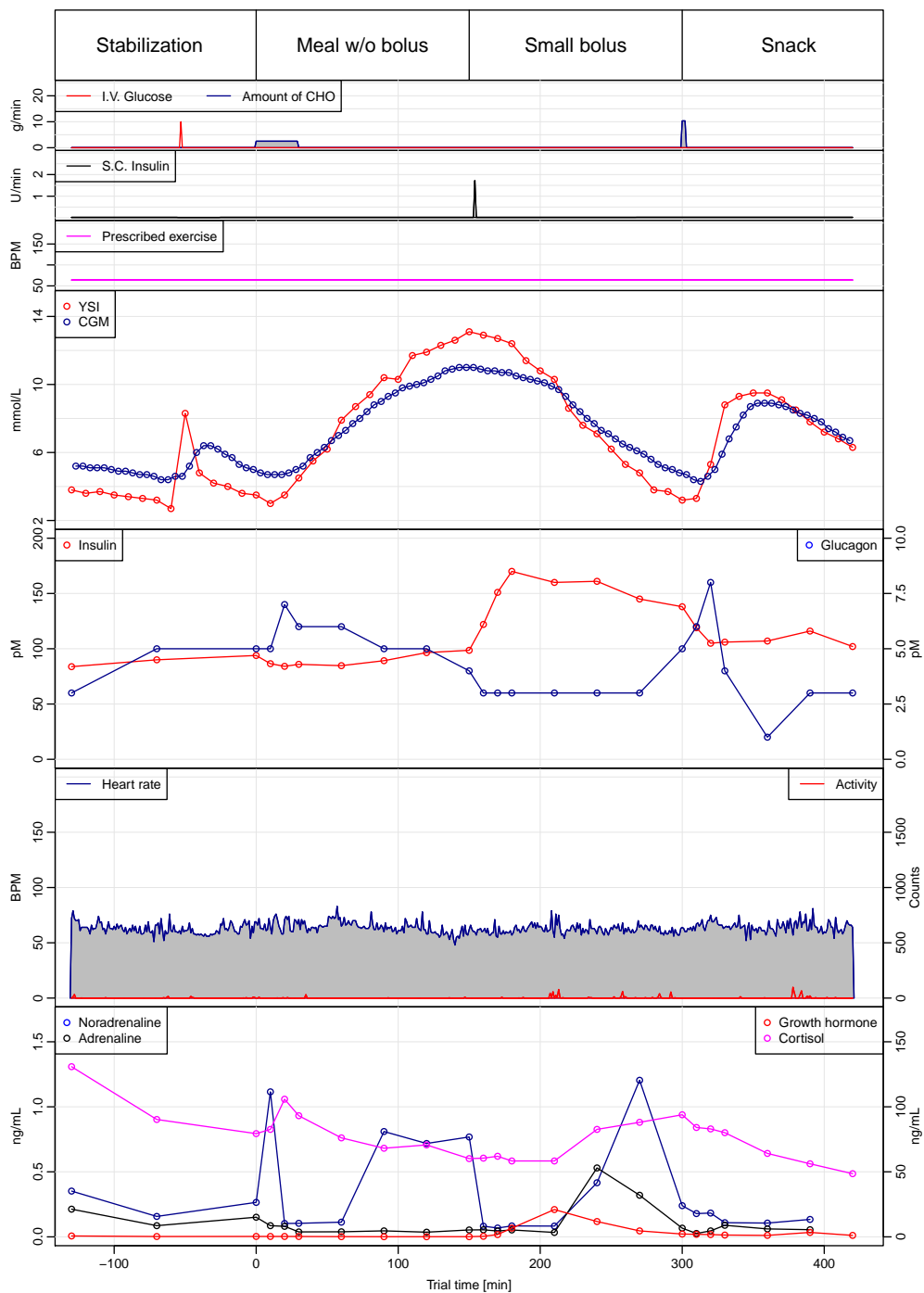


Figure 12: Results from trial 05b. Note that the S.C. insulin is above zero according to table II at all times even though it is hard to see.

Trial no. 06a

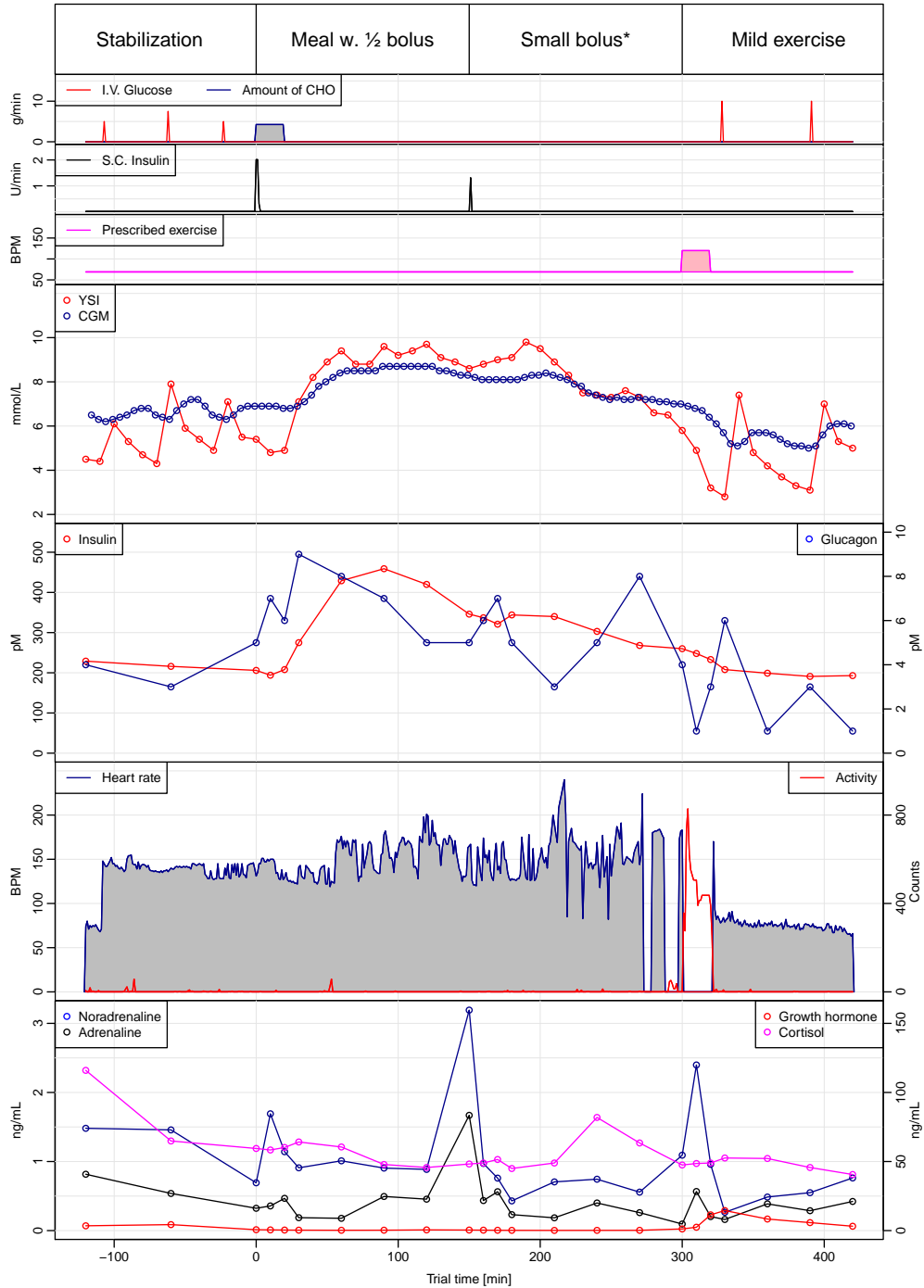


Figure 13: Results from trial 06a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 06b

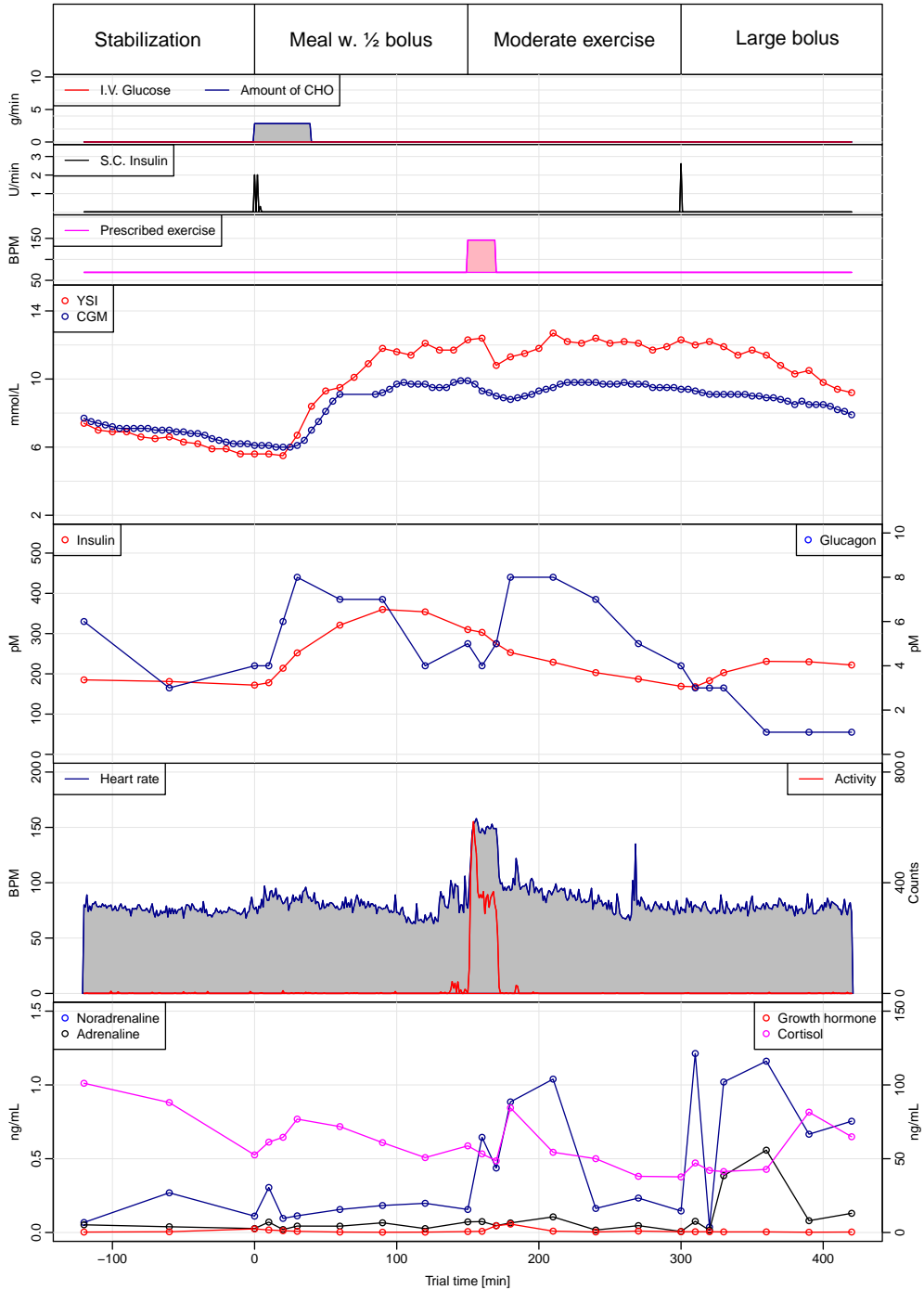


Figure 14: Results from trial 06b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 07a

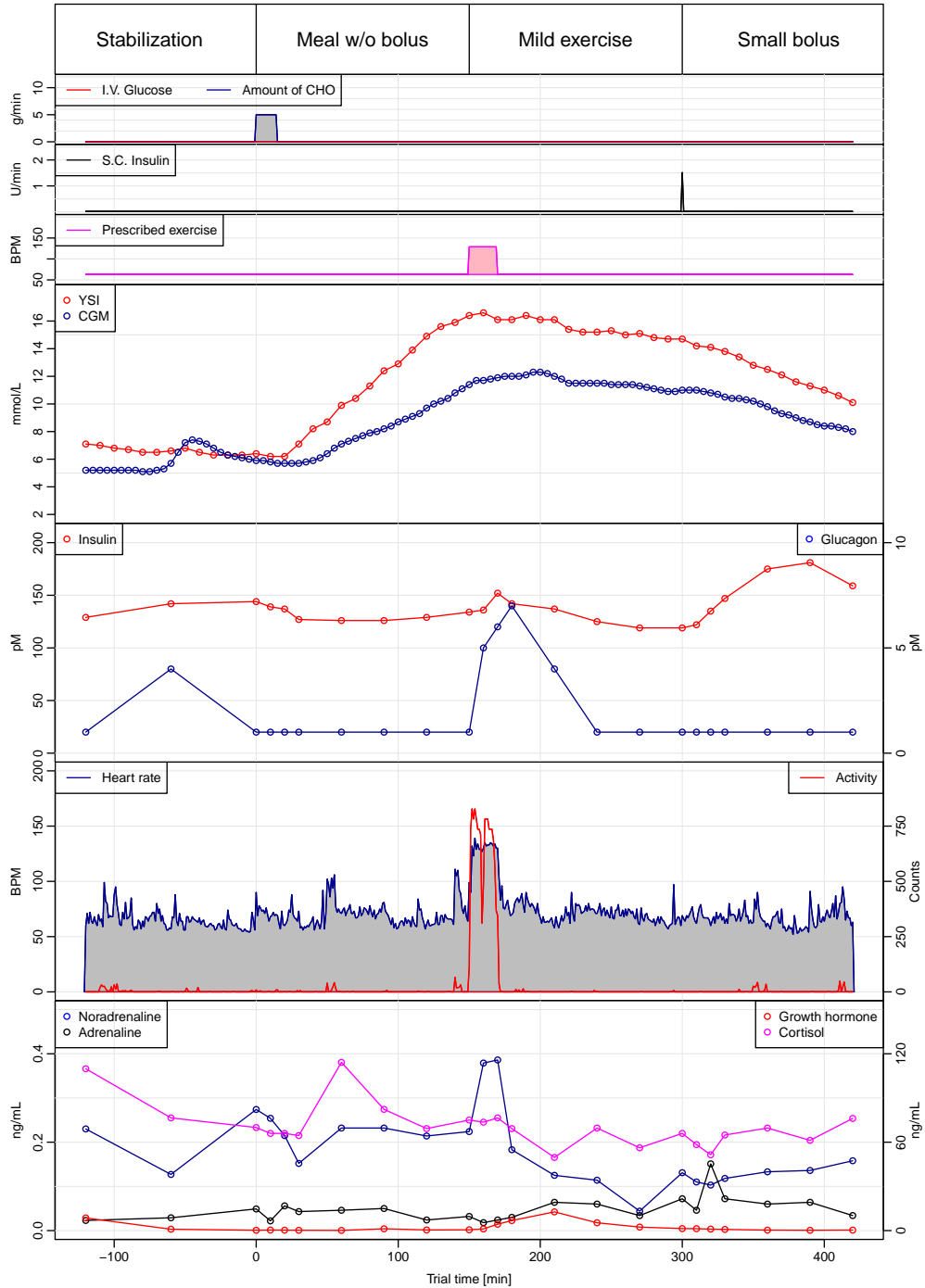


Figure 15: Results from trial 07a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 07b

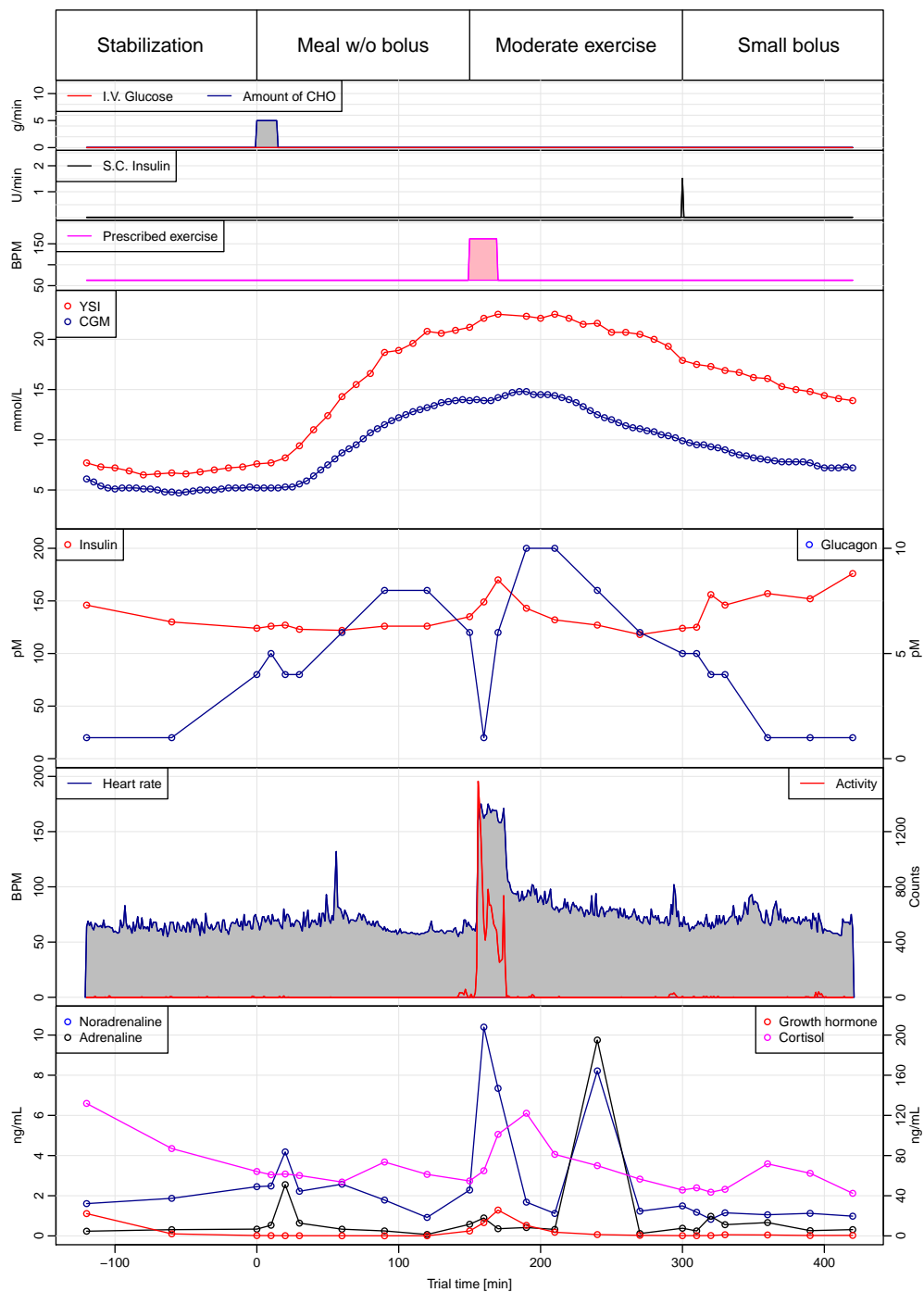


Figure 16: Results from trial 07b. Note that the S.C. insulin is above zero according to table II at all times even though it is hard to see.

Trial no. 08a

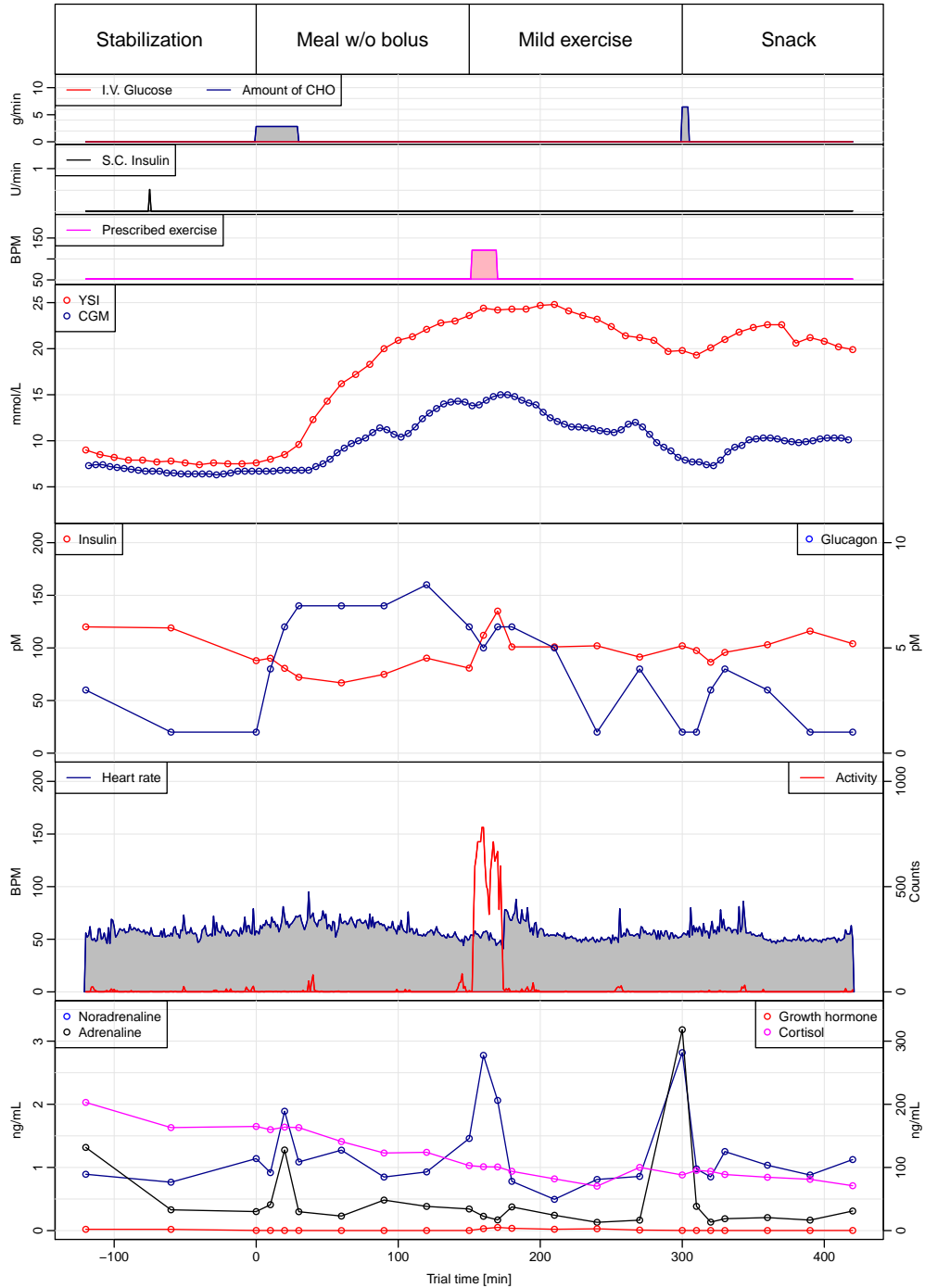


Figure 17: Results from trial 08a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 08b

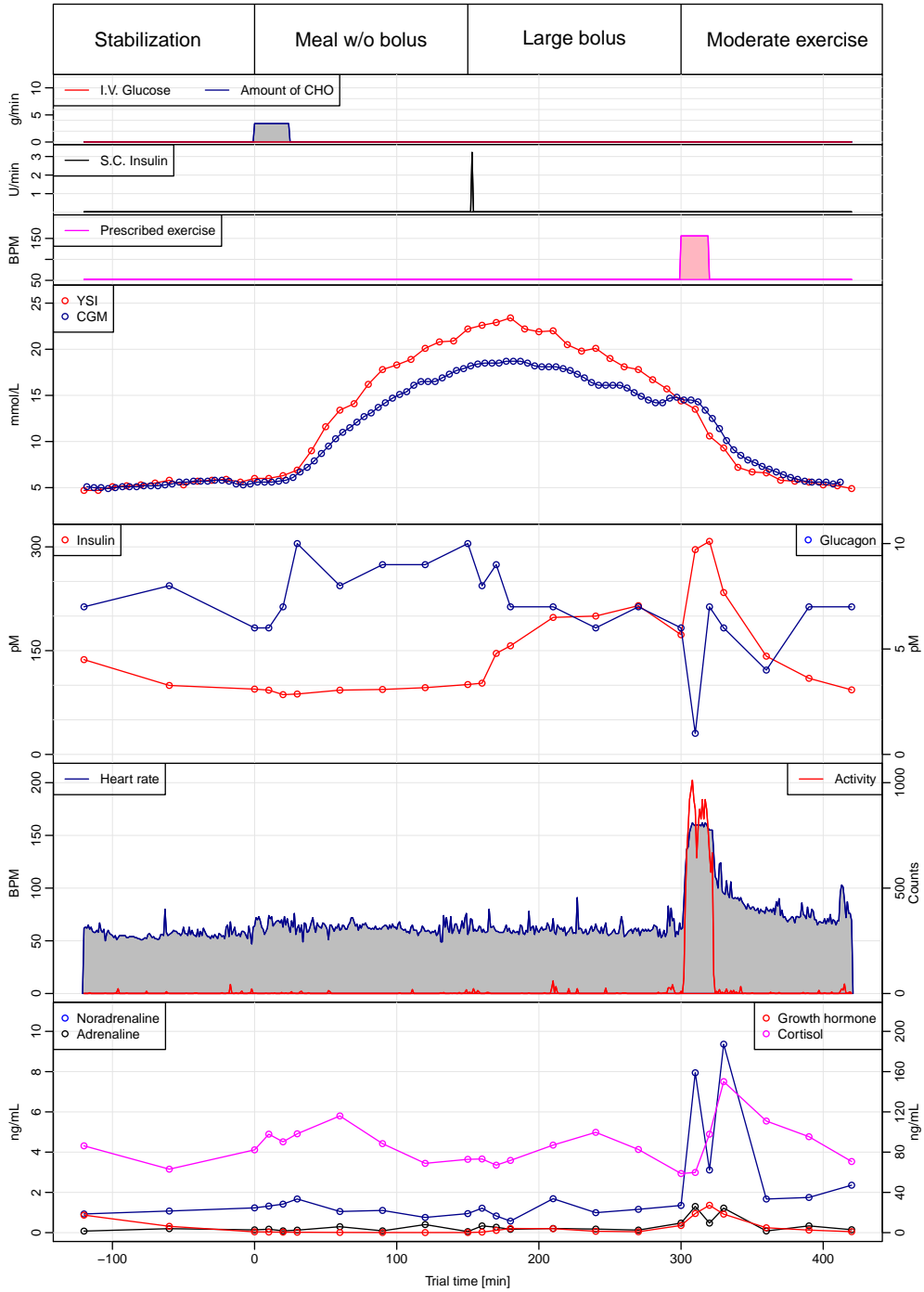


Figure 18: Results from trial 08b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 10a

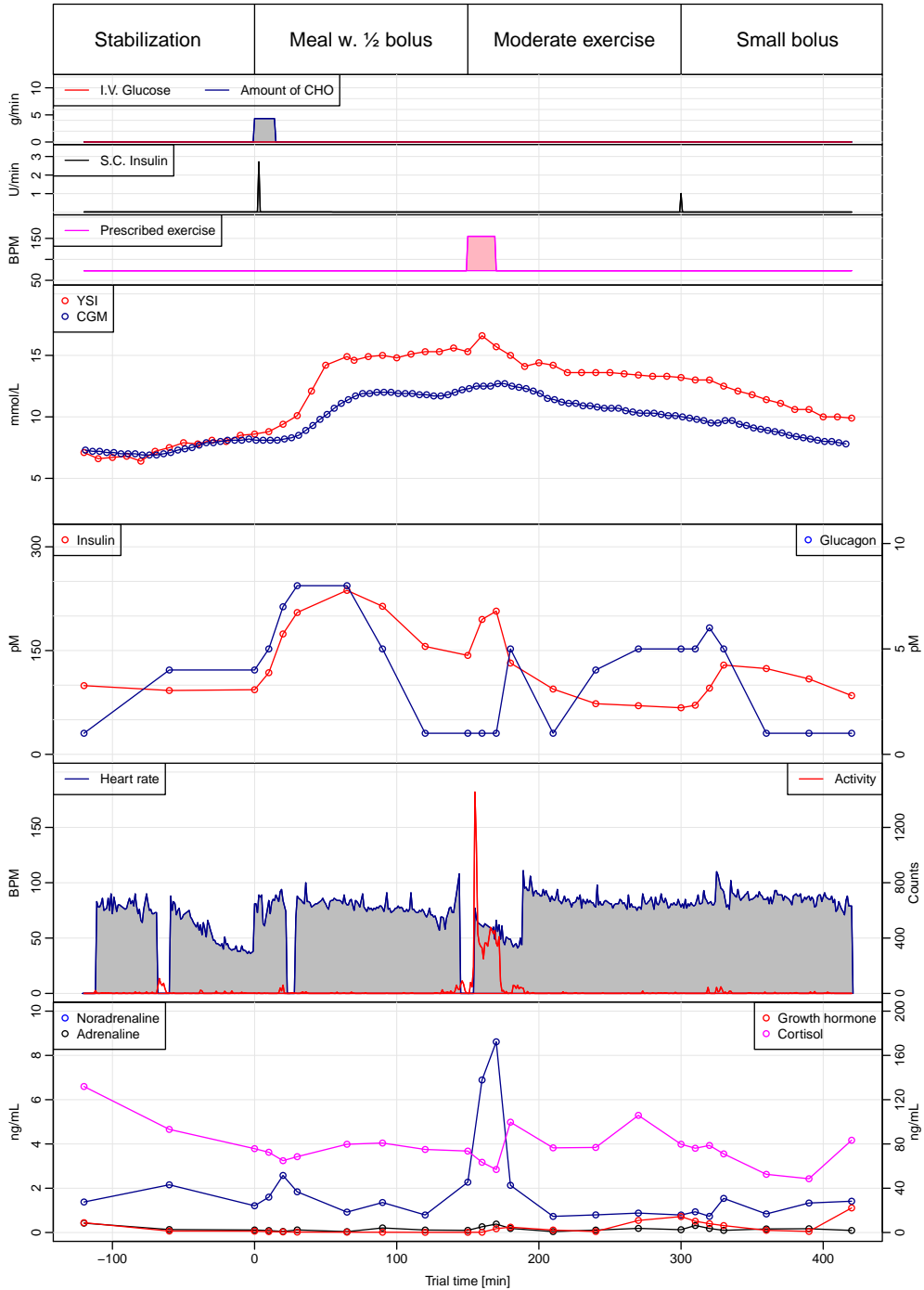


Figure 19: Results from trial 10a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 10b

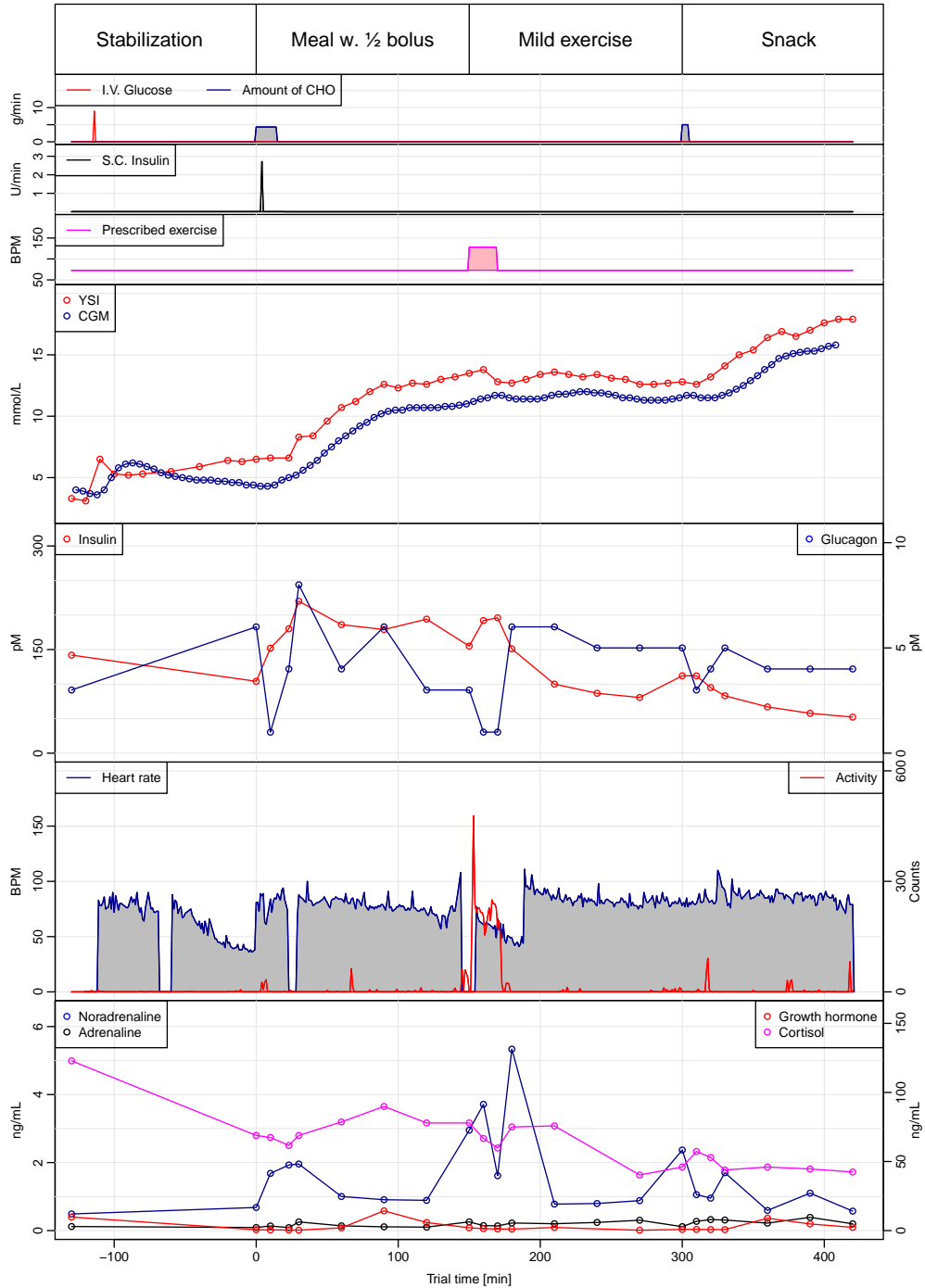


Figure 20: Results from trial 10b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 11a

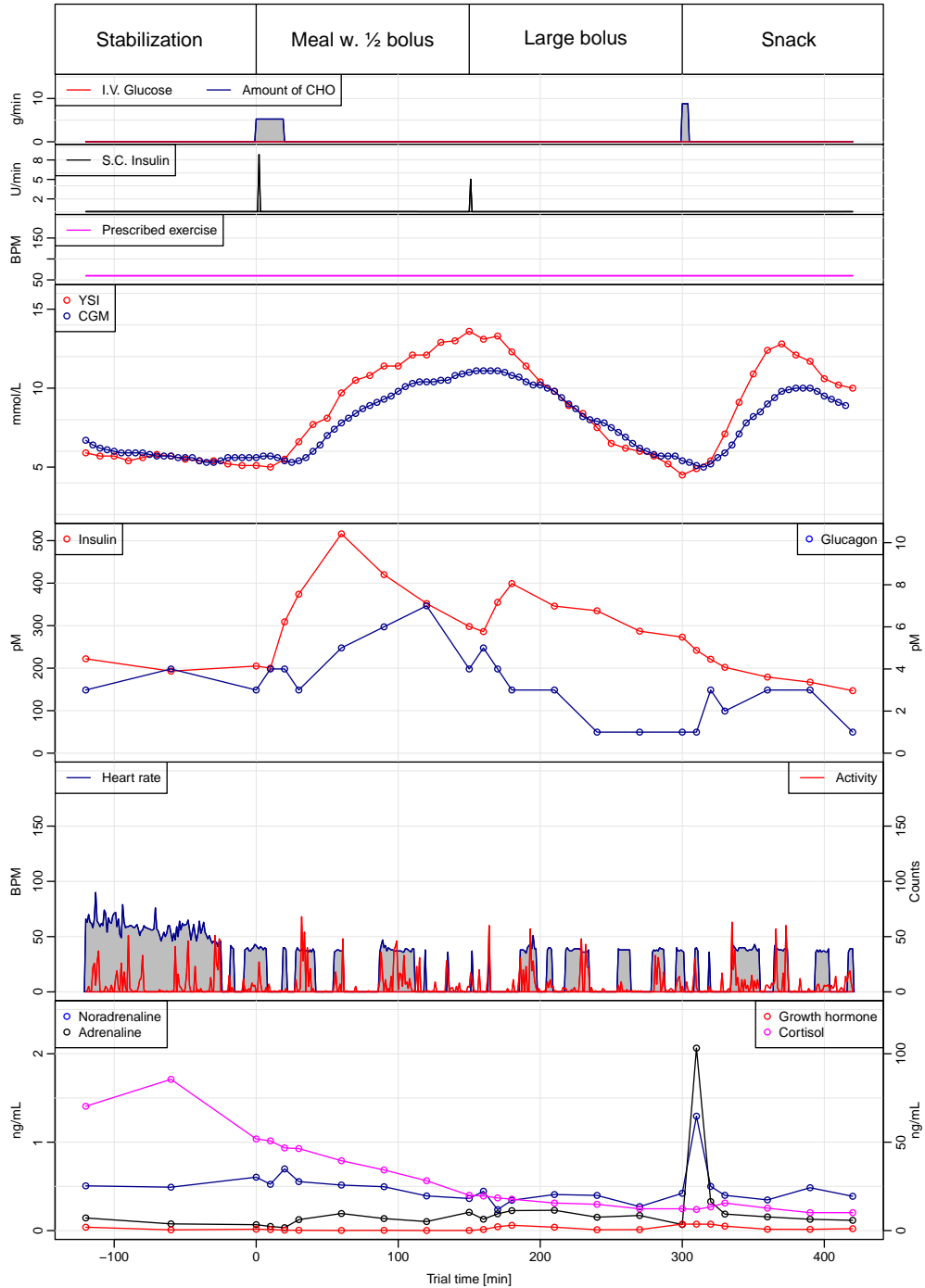


Figure 21: Results from trial 11a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 11b

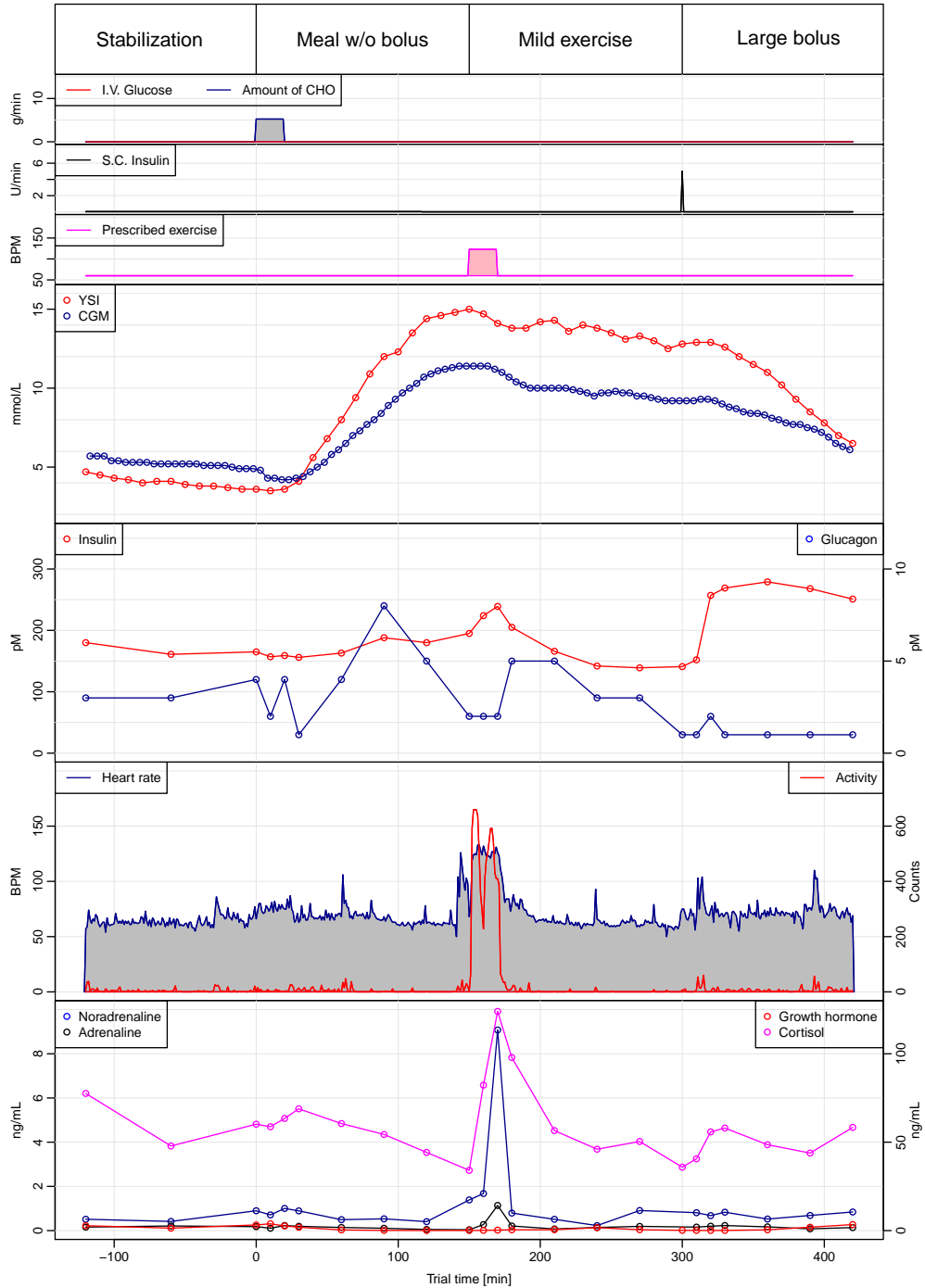


Figure 22: Results from trial 11b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 12a

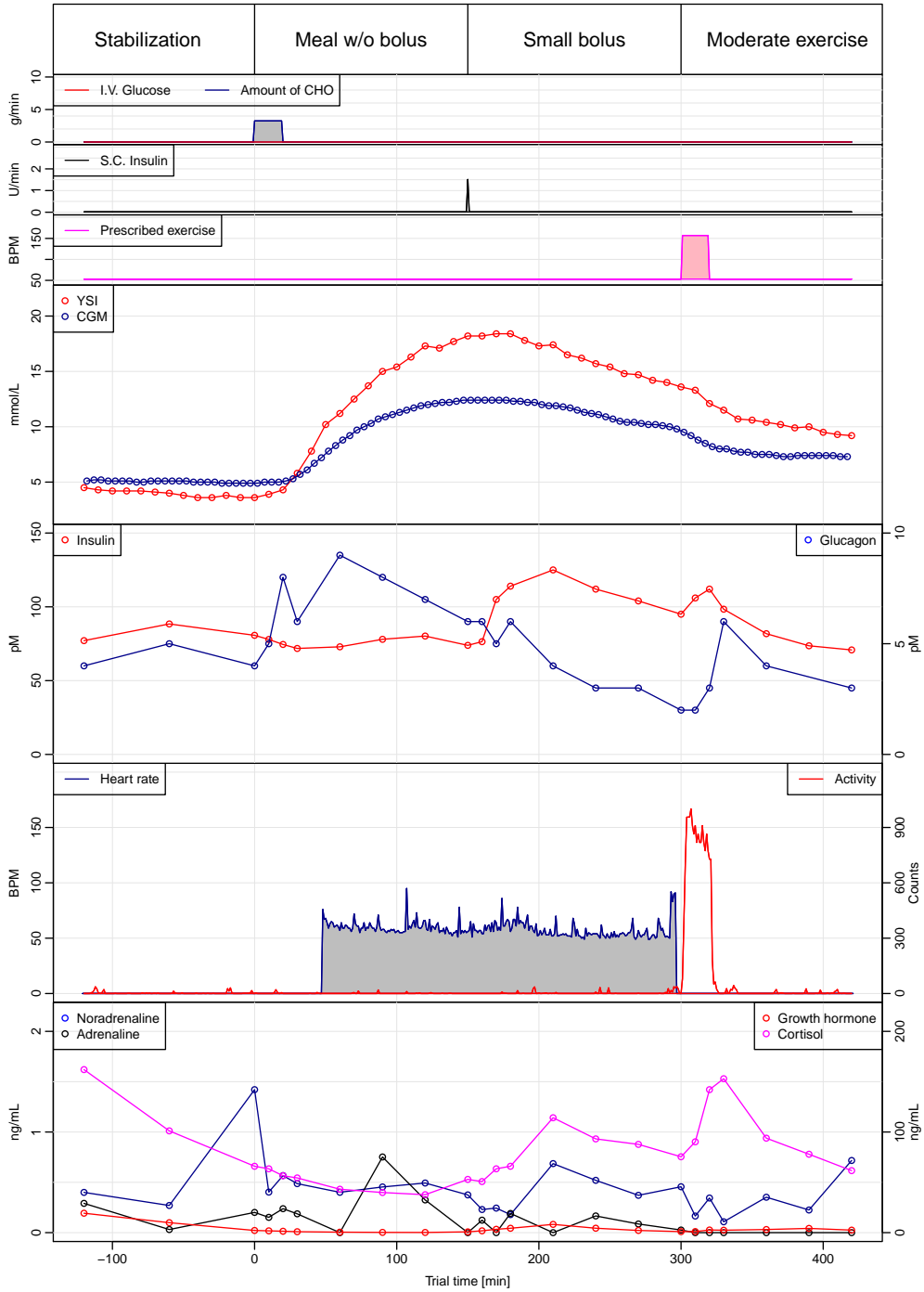


Figure 23: Results from trial 12a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 12b

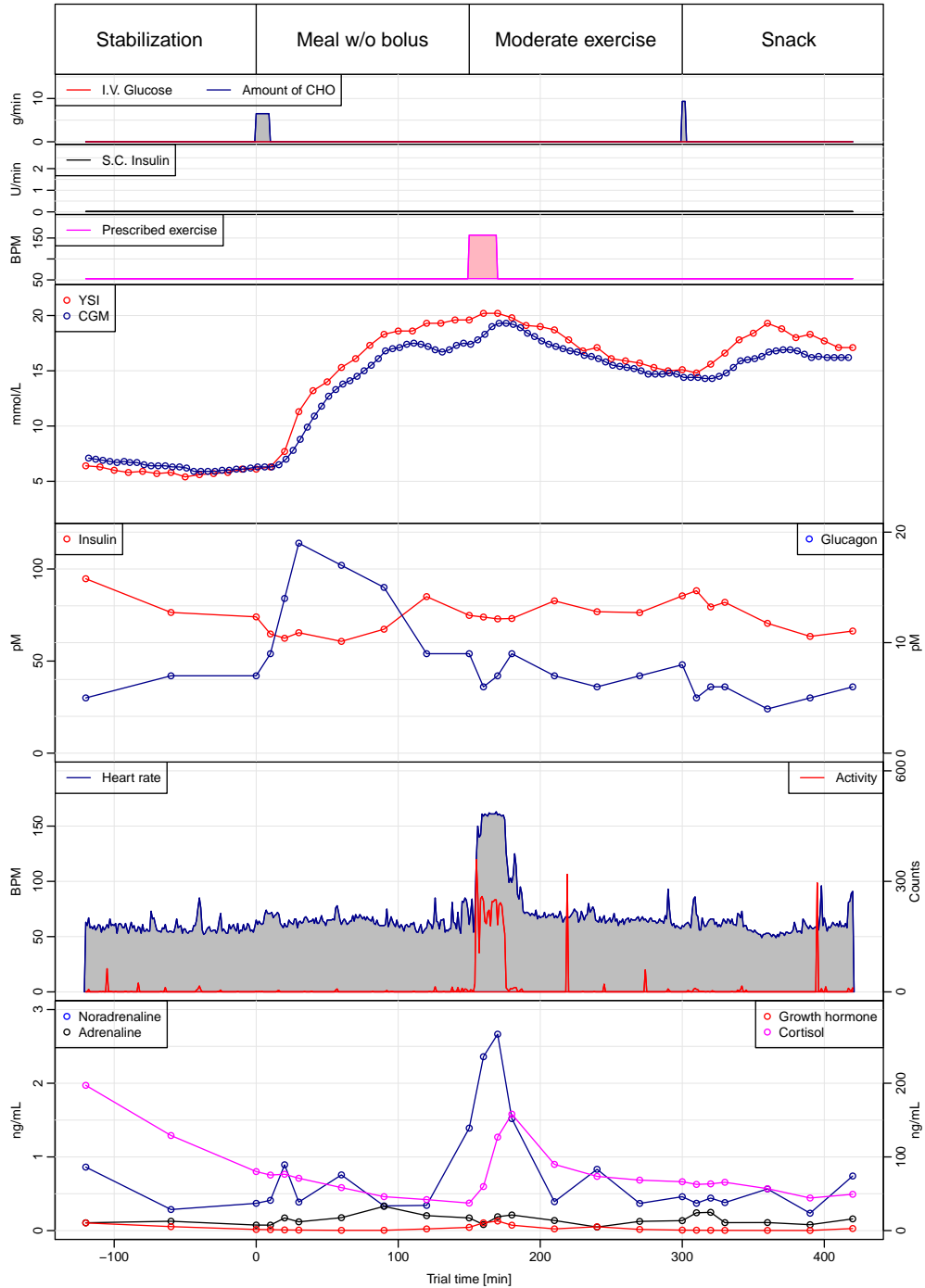


Figure 24: Results from trial 12b. Note that the S.C. insulin is above zero according to the info file.

Trial no. 13a

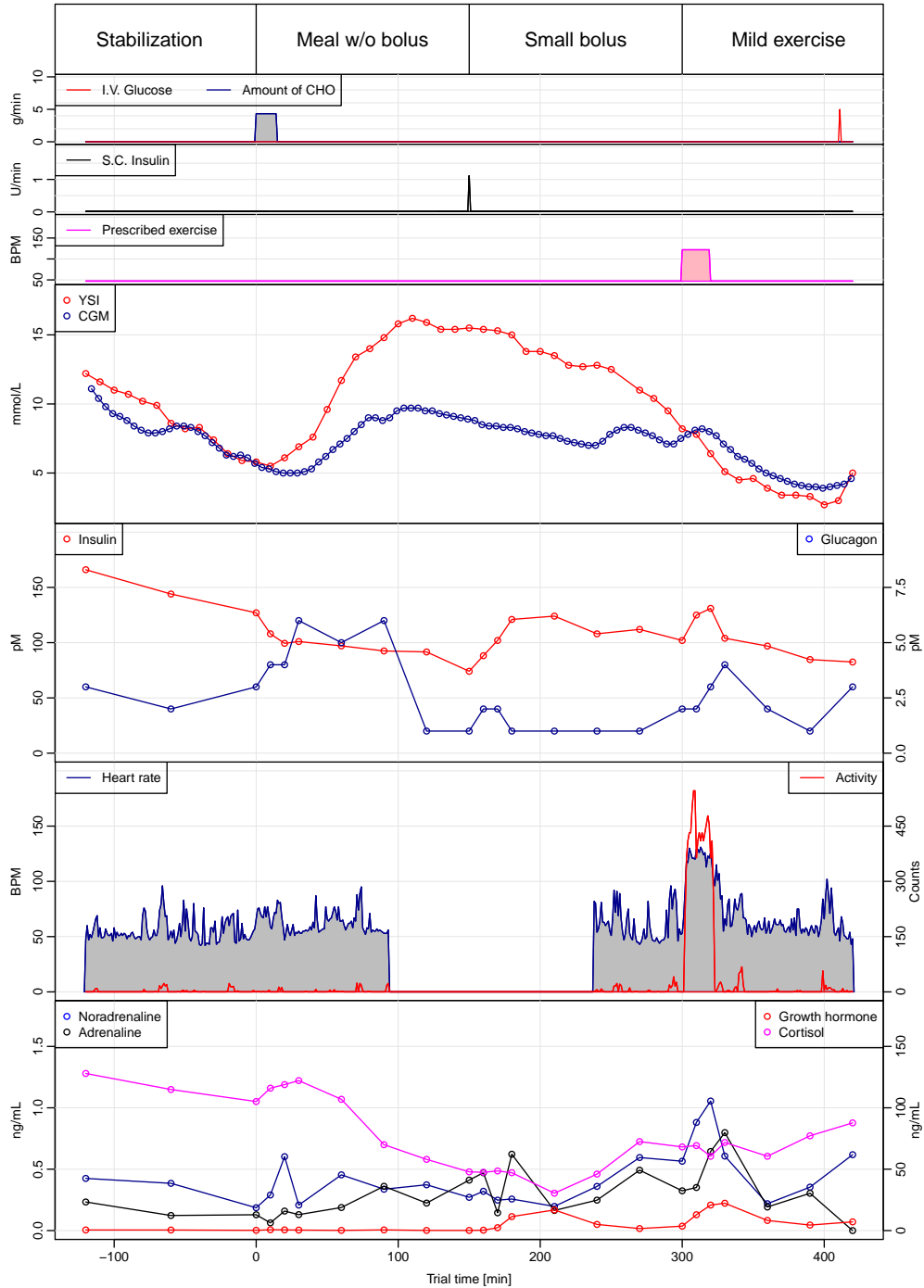


Figure 25: Results from trial 13a. Note that the S.C. insulin is above zero according to the info file.

Trial no. 13b

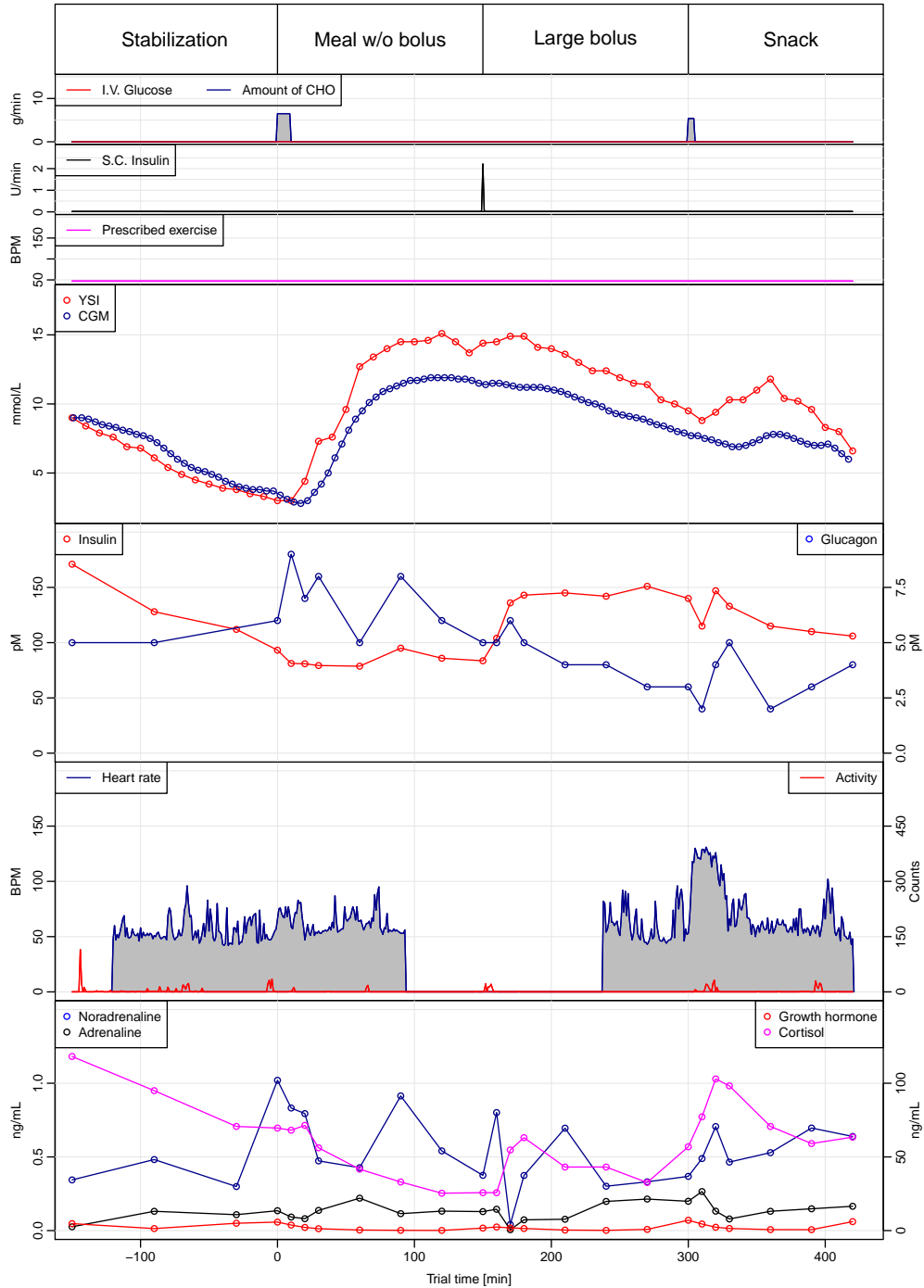


Figure 26: Results from trial 13b. Note that the S.C. insulin is above zero according to the info file.

References

- [1] R. Rowlett and the University of North Carolina at Chapel Hill. Si units for clinical data. http://www.unc.edu/~rowlett/units/scales/clinical_data.html Accessed January 3rd 2013.
- [2] S. Schmidt, D. Finan, A. Duun-Henriksen, J. Jørgensen, H. Madsen, H. Bengtsson, J. Holst, S. Madsbad, and K. Nørgaard. Effects of everyday life events on glucose, insulin, and glucagon dynamics in continuous subcutaneous insulin infusion-treated type 1 diabetes: Collection of clinical data for glucose modeling. *Diabetes technology & therapeutics*, 14(3):210–217, 2012.