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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: **Home use of a bihormonal bionic pancreas vs insulin pump therapy in adults with type 1 diabetes: A multicenter randomized clinical trial**

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METHODS

Institutional and regulatory oversight

In addition to institutional review board (IRB) oversight from the Partners Human Research Committee (Massachusetts General Hospital), Boston University, University of Massachusetts, University of North Carolina and Stanford University, the study was conducted under United States Food and Drug Administration Investigational Device Exemption #G140045, which was approved by the Office of In Vitro Diagnostics and Radiological Health within the Center for Devices and Radiological Health. We received an Investigational New Drug Exemption from the FDA for using glucagon in a pump for up to 27 hours. The study was overseen by an independent data safety monitoring board at Massachusetts General Hospital. Companies providing device components and in-kind support had no role in the design, conduct, analysis, or decision to publish the study.

Eligibility criteria

Key exclusion criteria included hepatic dialysis or renal failure, known coronary disease or abnormal electrocardiogram suggestive of coronary disease, congestive heart failure, history of cerebrovascular disease, hypoglycemic seizure in the last year, current participation in another diabetes-related clinical trial that, in the opinion of the principal investigator, would compromise the results of the study or subject safety, pregnancy, need to go outside of the designated geographic boundaries during either period of the study, current alcohol abuse, use of marijuana within 1 month of enrollment, or other substance abuse, personal history of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, seizure disorder, history of any non-hypoglycemic seizure within the last two years, or ongoing treatment with anticonvulsants, history of pheochromocytoma, history of adrenal disease and tumor, hypertension with systolic blood pressure greater than 160 mm Hg or diastolic greater than 100 mm Hg despite treatment, untreated or inadequately treated mental illness, or treatment with second generation anti-psychotic medications known to affect glucose regulation, electrically powered implants that may be susceptible to radio-frequency interference, history of adverse reaction to glucagon including allergy besides nausea and vomiting, history of established allergy or severe reaction to adhesive or tape that must be used in the study, history of eating disorder in the last two years such as anorexia, bulimia, or diabulemia, omission of insulin to manipulate weight, use of oral medications that assist in glycemic control, or live in or frequent areas with poor Verizon wireless network coverage which would prevent remote monitoring.

Hemoglobin A1c, glycemic stability or major or minor hypoglycemia were not included in the exclusion criteria.

Experimental Protocol

If hyperglycemia $>$16.7 mmol/l occurred, participants were instructed to inspect their insulin infusion set and replace it if there was doubt regarding its integrity. If hypoglycemia occurred during the BP arm, participants were instructed to inspect their glucagon infusion set and replace it if there was doubt regarding its integrity.

Laboratory tests drawn on day 1 and 12 of both the bionic pancreas and the comparator periods were: sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, magnesium, phosphorus, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, creatine phosphokinase, lactate dehydrogenase, uric acid, total protein, albumin, globulin high sensitivity c-reactive protein, total cholesterol, and high density lipoprotein.

Adverse events were reported by the participants during both arms of the study via a daily e-mail survey sent out every evening using REDCap (Research Electronic Data Capture).[6] REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The survey including asking the participants: how many symptomatic hypoglycemic events had occurred and how many grams

of carbohydrates were used in treating the hypoglycemia, duration of any exercise, the number of alcoholic drinks consumed, whether they had experienced any nausea (and if so, its intensity on a visual analog scale from 1 to 10), whether they had made any unscheduled infusion set changes, and whether they had used their own unblinded CGM during the comparator arm. About 99% (423/429) of surveys were completed during the bionic pancreas period, compared with 97% (416/429) of surveys in the comparator period. All reported episodes of hypoglycemia were associated with mild symptoms and treated with oral carbohydrates by the participants.

Pre-specified Secondary Outcomes

Pre-specified secondary outcomes included the percentage of time CGM glucose levels were in clinically relevant ranges, the number of symptomatic hypoglycemic events, the number of carbohydrate interventions for hypoglycemia, and the amount of carbohydrates taken for treatment of hypoglycemia. All glycemic outcome measures were calculated for the full 24-hour period and for the nighttime period (11:00 PM–7:00 AM). The number of participants with a mean CGM glucose level $\leq$8.6 mmol/l was determined, because this is the estimated average glucose that corresponds to a hemoglobin A1c of 7.0%.[7,8] To quantify adaptation by the BP, we compared results from Day 1 with Days 2–11. The mean of daily differences was calculated as described.[9,10] Other outcomes included insulin and glucagon total daily dose. Safety outcomes included nausea reported on the daily surveys, change in body mass, and change in laboratory measurements from the beginning to end of each study arm.

Table S1. Effect of participant characteristics on treatment effects.

Effect of baseline characteristics on treatment effects for mean glucose

Effect	Estimated interaction term between the effect and treatment arm with 95% CI	p-value
Age	0.172 (-0.358, 0.703)	0.52
Baseline HbA1c	-14.460 (-19.190, -9.729)	0.0026
Gender (female)	-8.159 (-23.444, 7.126)	0.30
T1D duration	0.542 (-0.138, 1.221)	0.15
Baseline insulin total daily dose	34.903 (-27.023, 96.830)	0.27
Percent of days using unblinded CGM during comparator arm	3.525 (-10.139, 17.188)	0.62

Effect of baseline characteristics on the treatment effect for percent of time <3.3 mmol/l

Effect	Estimated interaction term between the effect and treatment arm with 95% CI	p-value
Age	0.025 (-0.087, 0.012)	0.14
Baseline HbA1c	0.598 (0.043, 1.153)	0.035
Gender (female)	0.766 (-0.208, 1.739)	0.13
T1D Duration	-0.067 (-0.113, -0.021)	0.016
Baseline insulin total daily dose	1.976 (-3.052, 7.004)	0.47
Percent of days using unblinded CGM during comparator arm	-0.227 (-1.336, 0.882)	0.69

Table S2. Mean number of times per day carbohydrates were taken to treat hypoglycemia.

ID	Bionic Pancreas	Comparator
MGH01	0.82	1.09
MGH03	0.09	0.91
MGH04	0.27	0.73
MGH06	0.55	1.82
MGH07	0.18	0.45
MGH08	0.55	1.64
MGH10	0.18	0.36
MGH12	0.82	0.18
MGH13	1.27	0.27
MGH14	0.36	0.36
UMA02	0.18	0.91
UMA03	0.00	0.36
UMA04	0.09	0.45
UMA05	0.64	1.91
UMA06	0.18	0.73
UMA07	0.00	0.55
UMA08	0.27	0.82
UMA09	0.00	0.00
UMA10	0.36	0.64
UMA11	0.09	0.36
STA01	0.27	2.18
STA02	0.91	0.55
STA03	0.45	0.55
STA05	0.45	0.64
STA06	0.18	0.73
STA07	0.36	0.73
STA08	0.00	1.64
STA09	0.18	0.27
STA10	0.45	1.18
STA11	0.73	0.36
UNC02	0.73	1.00
UNC03	0.36	1.27
UNC04	1.27	2.55
UNC05	0.45	0.36
UNC06	0.00	1.18
UNC07	0.73	0.18
UNC08	0.00	1.73
UNC09	0.00	2.00
UNC10	0.73	3.00
Mean	0.39	0.94
SD	0.34	0.71
Min	0.00	0.00
Max	1.27	3.00

Table S3. Total daily dose of insulin in all participants and in participants with mean CGM glucose $\leq$8.6 mmol/l

ID	Bionic Pancreas		Comparator (all)		ID	Bionic Pancreas		Comparator (CGMG<8.6)	
	CGMG, mmol/l	TDD, U/kg	CGMG, mmol/l	TDD, U/kg		CGMG, mmol/l	TDD, U/kg	CGMG, mmol/l	TDD, U/kg
MGH01	7.4	0.59	7.7	0.54	MGH01	7.4	0.59	7.7	0.54
MGH03	7.3	0.56	7.3	0.62	MGH03	7.3	0.56	7.3	0.62
MGH04	7.6	0.64	7.7	0.59	MGH04	7.6	0.64	7.7	0.59
MGH06	7.9	0.65	9.8	0.49	MGH07	7.4	0.59	8.4	0.56
MGH07	7.4	0.59	8.4	0.56	UMA02	7.9	0.74	7.8	0.68
MGH08	7.6	0.51	9.2	0.49	UMA05	8.2	0.70	7.5	0.74
MGH10	7.6	0.57	9.1	0.49	UMA08	8.2	0.92	7.8	0.95
MGH12	8.2	0.74	12.5	0.51	STA01	8.5	0.88	8.2	1.02
MGH13	7.7	0.64	8.8	0.42	STA05	7.4	0.54	8.2	0.59
MGH14	8.8	0.97	9.7	0.89	STA07	7.6	0.62	7.9	0.66
UMA02	7.9	0.74	7.8	0.68	STA08	7.3	0.55	7.9	0.42
UMA03	8.5	0.71	9.6	0.70	STA11	7.5	0.61	8.4	0.57
UMA04	7.7	0.71	9.1	0.44	UNC03	8.1	0.70	7.7	0.55
UMA05	8.2	0.70	7.5	0.74	UNC04	7.2	0.52	7.1	0.47
UMA06	7.7	0.54	8.9	0.63	UNC07	8.3	0.47	10.0	0.46
UMA07	7.8	0.68	8.6	0.78	UNC08	6.3	0.26	5.2	0.26
UMA08	8.2	0.92	7.8	0.95	UNC10	7.1	0.53	7.5	0.59
UMA09	8.8	1.07	9.3	1.22					
UMA10	9.2	0.76	12.8	0.75	**Mean**	**7.6**	**0.61**	**7.8**	**0.60**
UMA11	7.6	0.66	9.3	0.68	**STD**	**0.5**	**0.15**	**0.9**	**0.18**
STA01	8.5	0.88	8.2	1.02	**Min**	**6.3**	**0.26**	**5.2**	**0.26**
STA02	7.4	0.60	9.8	0.68	**Max**	**8.5**	**0.92**	**10.0**	**1.02**
STA03	7.9	0.67	11.2	0.48	***p***	**0.2845**	**0.6536**		
STA05	7.4	0.54	8.2	0.59					
STA06	8.1	0.67	8.6	0.66					
STA07	7.6	0.62	7.9	0.66					
STA08	7.3	0.55	7.9	0.42					
STA09	7.9	0.64	13.6	0.48					
STA10	7.5	0.63	9.8	0.55					
STA11	7.5	0.61	8.4	0.57					
UNC02	7.7	0.59	9.1	0.54					
UNC03	8.1	0.70	7.7	0.55					
UNC04	7.2	0.52	7.1	0.47					
UNC05	8.2	0.64	9.0	0.58					
UNC06	8.4	0.83	9.4	0.68					
UNC07	8.3	0.47	10.0	0.46					
UNC08	6.3	0.26	5.2	0.26					
UNC09	8.4	0.93	10.2	0.79					
UNC10	7.1	0.53	7.5	0.59					
Mean	**7.8**	**0.66**	**9.0**	**0.62**					
STD	**0.6**	**0.15**	**1.6**	**0.18**					
Min	**6.3**	**0.26**	**5.2**	**0.26**					
Max	**9.2**	**1.07**	**13.6**	**1.22**					
p	**0.0000**	**0.0143**							

Table S4. Number of user-initiated insulin doses.

	Bionic Pancreas Meal announcements per day	**Comparator** Insulin boluses per day (meal and correction)	**Difference**
MGH01	2.4	7.4	-5
MGH03	2.9	6.8	-3.9
MGH04	3	6.7	-3.7
MGH06	2.4	5.3	-2.9
MGH07	2.9	5.6	-2.7
MGH08	2.5	5.9	-3.4
MGH10	1.4	7.4	-6
MGH12	2.8	6.1	-3.3
MGH13	3.2	4.4	-1.2
MGH14	2	5.3	-3.3
UMA02	3.1	11.4	-8.3
UMA03	2.7	6.9	-4.2
UMA04	3.4	2.1	1.3
UMA05	2.2	3.5	-1.3
UMA06	2.3	7.1	-4.8
UMA07	2.7	3.7	-1
UMA08	3	6.9	-3.9
UMA09	3.5	2.9	0.6
UMA10	1.3	2.9	-1.6
UMA11	3.5	6.3	-2.8
STA01	5.5	4.7	0.8
STA02	4.1	6.5	-2.4
STA03	2.4	5	-2.6
STA05	2.7	5.7	-3
STA06	2.6	4.1	-1.5
STA07	3	3.3	-0.3
STA08	2.8	5.3	-2.5
STA09	1.4	8.2	-6.8
STA10	2.8	4.5	-1.7
STA11	2.5	6.8	-4.3
UNC02	1.4	4.9	-3.5
UNC03	2.1	3.1	-1
UNC04	3	7.5	-4.5
UNC05	1.4	12.1	-10.7
UNC06	2.2	3.3	-1.1
UNC07	2	7.5	-5.5
UNC08	2.3	4.3	-2
UNC09	2	3	-1
UNC10	2.8	4.1	-1.3
Mean	2.6	5.6	-3.0
STD	0.8	2.2	2.4
Min	1.3	2.1	-10.7
Max	5.5	12.1	1.3

Table S5. Mean nausea scores on a visual analog scale from 0–10 by day and sex.

	Bionic Pancreas			Comparator		
Day	**Male**	**Female**	**Both**	**Male**	**Female**	**Both**
1	0.33	1.19	0.79	0	0	0
2	0	0.86	0.46	0.17	0	0.08
3	0.44	0.67	0.56	0.06	0	0.03
4	0.22	0.57	0.41	0.17	0.1	0.13
5	0.06	0.57	0.33	0	0	0
6	0.67	0.48	0.56	0	0	0
7	0.44	0.52	0.49	0.06	0	0.03
8	0.06	1.19	0.67	0.06	0.1	0.08
9	0.33	0.52	0.44	0.06	0.14	0.1
10	0.22	0.9	0.59	0.06	0.1	0.08
11	0.11	0.43	0.28	0.06	0	0.03
Mean	**0.26**	**0.72**	**0.51**	**0.06**	**0.04**	**0.05**
p	0.0188	0.0000	0.0000			

Nausea was self-reported daily as a whole integer value on a visual analog score from 0–10.

Table S6. Change in laboratory test value through each study arm, and p-value for the difference in the changes between the two study arms.

	Bionic Pancreas (BP)	Comparator	BP vs. Comparator
	Mean (SD)	Mean (SD)	*p*-value
Amylase	2.03 (13.25)	0.49 (10.59)	0.550
Albumin	0 (0.24)	0.023 (0.35)	0.755
Alkalin Phosphatase	-2.85 (8.55)	-3.15 (9.85)	0.893
BUN	1.44 (2.85)	0.10 (3.20)	0.073
Calcium	-0.0026 (0.42)	0.079 (0.42)	0.431
Chloride	0.76 (3.38)	-0.39 (3.30)	0.061
CO2	-1.26 (4.58)	-0.15 (6.06)	0.398
Creatinine	0.0056 (0.13)	0.0028205 (0.0996295)	0.909
eGFR	-1.86 (12.63)	-0.77 (10.75)	0.576
Globulin	-0.085 (0.33)	0.01 (0.23)	0.141
Potassium	-0.032 (0.34)	-0.16 (0.28)	0.081
Sodium	0.55 (3.37)	-0.53 (3.11)	0.137
Plasma Glucose	-16.46 (89.69)	-28 (89.92)	0.571
SGOT	0.56 (3.94)	0.103 (10.05)	0.808
SGPT	0.28 (6.52)	-0.95 (5.088)	0.277
Total Bilirubin	-0.041 (0.22)	-0.021 (0.22)	0.690
Total Protein	-0.031(0.36)	0.033 (0.49)	0.552
CPK	-12.97 (72.15)	-29.74 (95.76)	0.392
CRP HighSens	-1.83 (8.45)	0.14 (1.94)	0.226
Direct Bilirubin	-0.012 (0.06)	-0.0082 (0.083)	0.837
HCT	-0.73 (2.22)	0.049 (2.21)	0.100
HGB	-0.16 (0.68)	0.076 (0.68)	0.119
MCH	0.082 (0.62)	0.0051 (0.596)	0.625
MCHC	0.25 (1.027)	0.16 (0.77)	0.606
MCV	-0.47 (1.83)	-0.43 (1.20)	0.851
PLT	13.69 (26.24)	7.13 (35.63)	0.341
RBC	-0.054 (0.22)	0.027 (0.23)	0.106
RDW	0.033 (0.50)	0.082 (0.36)	0.582
WBC	1.079 (1.53)	0.47 (1.087)	**0.035**
LDH	0.59 (19.86)	-9.92 (25.61)	**0.035**
Total Cholesterol	-9.23 (18.86)	-0.41 (21.68)	0.07
Cardiac Risk Ratio	0.013 (0.089)	0.023 (0.090)	0.487
HDL Direct	-4.28 (7.62)	0.74 (10.85)	**0.023**
LDL Direct	-6.76 (16.98)	-2.92 (17.28)	0.344
Triglycerides	4.68 (42.79)	5.95 (39.020)	0.885
Lipase	1.38 (17.80)	0.90 (9.78)	0.860
Magnesium	0.036 (0.12)	0.020 (0.14)	0.551
Phosphorus	0.087 (0.63)	0.35 (0.69)	0.108
Uric Acid	0 (0.70)	-0.072 (0.65)	0.605

Table S7. Scheduled and unscheduled infusion set changes.

	Bionic Pancreas Glucagon		Bionic Pancreas Insulin		Comparator Insulin	
ID	Sheduled	Unscheduled	Sheduled	Unscheduled	Sheduled	Unscheduled
MGH-01	11	0	4	0	2	1
MGH-03	10	0	6	2	2	1
MGH-04	11	0	6	0	3	3
MGH-06	10	1	6	0	5	0
MGH-07	10	1	5	0	5	0
MGH-08	10	1	4	0	5	0
MGH-10	11	0	6	1	5	1
MGH-12	9	0	4	0	5	0
MGH-13	11	0	7	0	6	0
MGH-14	11	0	4	0	6	0
STA-01	11	1	5	0	4	2
STA-02	11	0	4	0	4	0
STA-03	10	0	5	0	3	0
STA-05	10	1	4	0	5	0
STA-06	10	0	4	0	3	1
STA-07	11	0	5	1	5	0
STA-08	11	0	5	0	4	0
STA-09	11	0	5	0	5	1
STA-10	9	1	4	1	3	2
STA-11	11	1	5	1	5	0
UMA-02	11	0	5	0	0	0
UMA-03	10	1	5	0	4	0
UMA-04	11	0	4	0	3	0
UMA-05	11	1	4	0	2	0
UMA-06	10	1	6	0	2	0
UMA-07	11	0	7	1	5	1
UMA-08	9	1	4	0	1	1
UMA-09	8	0	4	1	3	0
UMA-10	11	0	5	0	0	0
UMA-11	8	3	2	0	3	0
UNC-02	11	0	5	0	5	0
UNC-03	11	0	6	1	6	0
UNC-04	11	0	5	0	6	0
UNC-05	11	0	3	1	5	0
UNC-06	11	0	5	1	6	0
UNC-07	11	0	5	0	5	1
UNC-08	11	0	5	0	6	0
UNC-09	11	0	6	0	5	0
UNC-10	11	0	5	0	8	0
sum	408	14	189	11	160	15
% of total	97%	3%	95%	6%	91%	9%

Table S8. Instances of disconnection and offline time during both the comparator and bionic pancreas arms.

Participants were instructed to disconnect from the devices for swimming and bathing because the devices were not waterproof. Participants were also allowed to disconnect from the devices for exercise or other activities, but they were not to be disconnected from the devices by choice for more than 60 minutes at a time or more than a total of 120 minutes per 24 hour period, and they were not to treat themselves with insulin from another source when voluntarily disconnected. If the bionic pancreas was not working properly for an extended period of time then there was provision in the protocol for the subject to switch back to conventional insulin pump therapy until the bionic pancreas could be brought back online, but this did not happen during the trial.

Participants completed an email survey in the evening on each of 11 days in which they answered two questions regarding the amount of time the bionic pancreas with only the blinded CGM functionality operating (in the comparator arm) or the bionic pancreas (in the bionic pancreas arm) was either not worn by choice (one question) or was not working properly (a separate question) during the previous 24 hours. The exact wording of the questions was:

Estimate the total amount of time in minutes that you were NOT wearing the bionic pancreas by choice. Select from the drop down list.

0–15 minutes
16–30 minutes
31–45 minutes
46–60 minutes
61–75 minutes
76–90 minutes
91–105 minutes
106–120 minutes
More than 120 minutes

Estimate the total amount of time in minutes that the bionic pancreas wasn't working properly. Select from the drop down list.

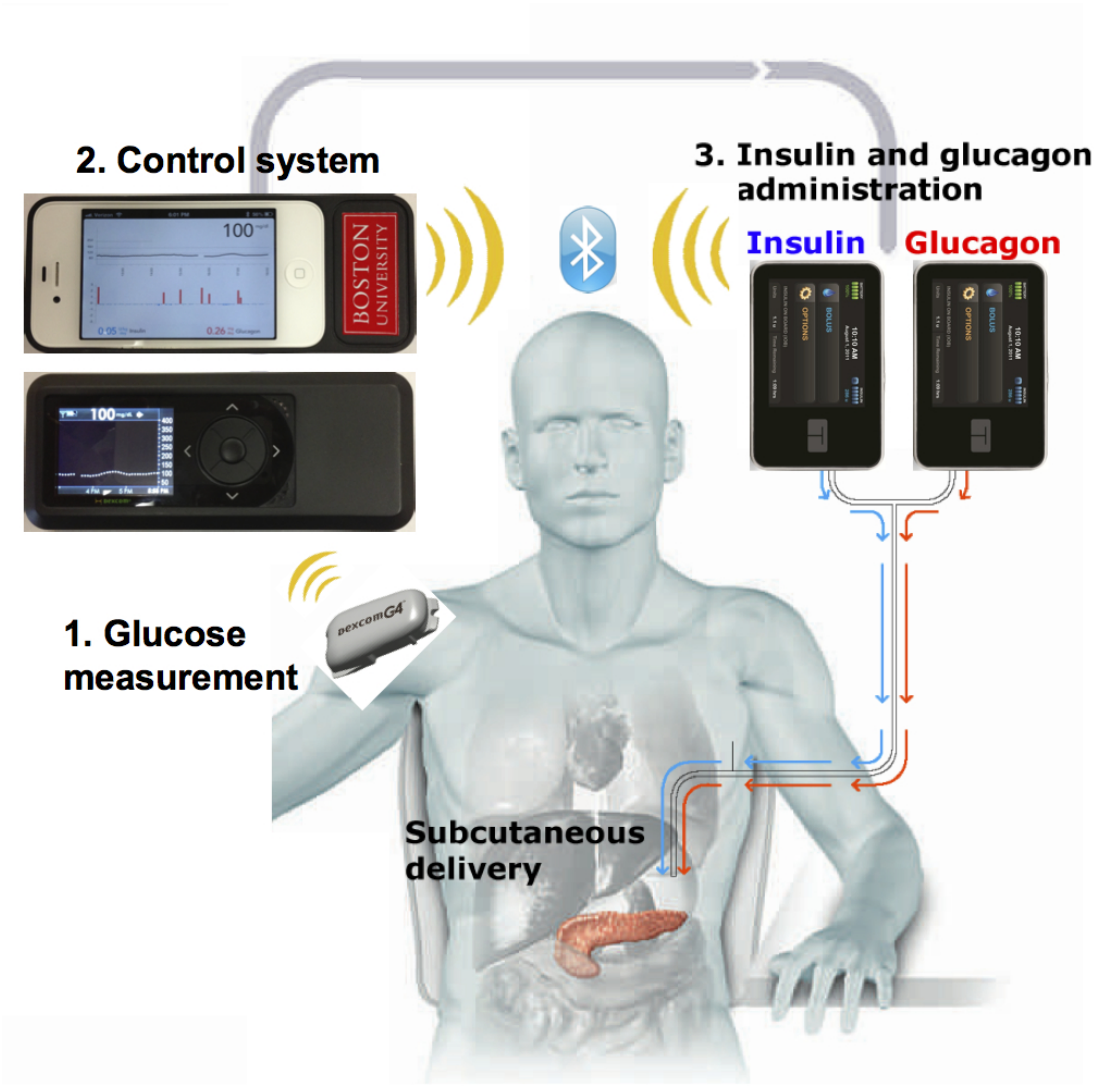
0–15 minutes
16–30 minutes
31–45 minutes
46–60 minutes
61–75 minutes
76–90 minutes
91–105 minutes
106–120 minutes
More than 120 minutes

If the CGM sensor needed to be replaced then there was a warm up period of at least 2 hours before the first calibration could be performed. When the CGM was not available the bionic pancreas would still deliver basal insulin, would respond to entered fingerstick BG measurement with insulin and/or glucagon administration as if they were CGM values, and would give meal-priming boluses of insulin in response to meal announcements. We did not provide specific guidance to participants regarding how periods without CGM signal were to be scored in the context of the daily surveys, so some participants may have scored this period as "bionic pancreas wasn't working properly".

If the subject answered this question on each day they should have a total of 11 entries. In some cases the number of entries is less than 11 because the subject did not return the entire survey or did not answer this specific question on one or more days. In the comparator and bionic pancreas arms the relevant questions were answered in 95.3% and 96.3% of possible instances, respectively. The total possible responses would be are 39 participants $\times$ 11 days = 429 possible responses in both cases.

Comparator "not wearing the bionic pancreas by choice"											Comparator "bionic pancreas wasn't working properly"								
Time (min)	**0-15**	**16-30**	**31-45**	**46-60**	**61-75**	**76-90**	**91-105**	**106-120**	**>120**		**0-15**	**16-30**	**31-45**	**46-60**	**61-75**	**76-90**	**91-105**	**106-120**	**>120**
MGH01	5	0	0	0	0	0	0	0	0		4	1	0	0	0	0	0	0	0
MGH03	10	1	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
MGH04	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
MGH06	10	0	0	1	0	0	0	0	0		11	0	0	0	0	0	0	0	0
MGH07	9	2	0	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
MGH08	8	0	0	0	0	0	0	0	0		8	0	0	0	0	0	0	0	0
MGH10	10	1	0	0	0	0	0	0	0		9	2	0	0	0	0	0	0	0
MGH12	9	0	0	0	0	0	0	0	0		9	0	0	0	0	0	0	0	0
MGH13	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
MGH14	10	0	1	0	0	0	0	0	0		10	0	0	1	0	0	0	0	0
STA01	11	0	0	0	0	0	0	0	0		8	3	0	0	0	0	0	0	0
STA02	8	0	0	0	0	0	0	0	1		7	2	0	0	0	0	0	0	0
STA03	11	0	0	0	0	0	0	0	0		10	0	1	0	0	0	0	0	0
STA05	11	0	0	0	0	0	0	0	0		9	1	0	1	0	0	0	0	0
STA06	7	4	0	0	0	0	0	0	0		10	0	0	0	0	1	0	0	0
STA07	10	1	0	0	0	0	0	0	0		6	2	2	0	0	0	0	1	0
STA08	11	0	0	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
STA09	11	0	0	0	0	0	0	0	0		10	0	0	0	0	0	0	1	0
STA10	9	0	0	0	0	0	0	0	0		9	0	0	0	0	0	0	0	0
STA11	9	0	0	0	0	0	0	0	0		9	0	0	0	0	0	0	0	0
UMA02	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UMA03	8	1	0	1	0	0	0	0	1		11	0	0	0	0	0	0	0	0
UMA04	9	0	0	0	0	0	0	0	1		9	0	0	0	0	0	1	0	0
UMA05	10	1	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UMA06	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UMA07	9	2	0	0	0	0	0	0	0		6	2	1	1	0	1	0	0	0
UMA08	11	0	0	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
UMA09	9	0	0	0	0	0	0	0	0		8	1	0	0	0	0	0	0	0
UMA10	10	1	0	0	0	0	0	0	0		9	0	1	0	0	1	0	0	0
UMA11	10	0	0	0	0	0	0	0	1		10	0	0	0	0	0	0	0	1
UNC02	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UNC03	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UNC04	10	1	0	0	0	0	0	0	0		9	2	0	0	0	0	0	0	0
UNC05	10	1	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UNC06	11	0	0	0	0	0	0	0	0		10	0	0	0	0	0	0	0	1
UNC07	8	2	1	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UNC08	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UNC09	11	0	0	0	0	0	0	0	0		9	1	0	0	0	0	0	1	0
UNC10	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
Sum	383	18	2	2	0	0	0	0	4		372	20	5	3	0	3	1	3	2
% total	**89.3**	**4.2**	**0.5**	**0.5**	**0**	**0**	**0**	**0**	**0.9**		**86.7**	**1.2**	**0.7**	**0**	**0**	**0.7**	**0.2**	**0.7**	**0.5**

	Bionic Pancreas "not wearing the bionic pancreas by choice"										Bionic Pancreas "bionic pancreas wasn't working properly"								
Time (min)	**0-15**	**16-30**	**31-45**	**46-60**	**61-75**	**76-90**	**91-105**	**106-120**	**>120**		**0-15**	**16-30**	**31-45**	**46-60**	**61-75**	**76-90**	**91-105**	**106-120**	**>120**
MGH01	9	2	0	0	0	0	0	0	0		10	0	1	0	0	0	0	0	0
MGH03	11	0	0	0	0	0	0	0	0		10	0	1	0	0	0	0	0	0
MGH04	11	0	0	0	0	0	0	0	0		6	2	2	1	0	0	0	0	0
MGH06	9	2	0	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
MGH07	10	0	0	0	0	0	0	0	0		6	2	0	0	0	1	0	0	1
MGH08	9	0	0	0	1	0	0	0	0		7	2	0	0	0	1	0	0	0
MGH10	3	7	0	0	0	0	0	0	0		10	0	0	0	0	0	0	0	0
MGH12	8	1	0	0	0	0	0	0	0		8	1	0	0	0	0	0	0	0
MGH13	10	0	0	0	0	0	0	0	0		9	1	0	0	0	0	0	0	0
MGH14	10	1	0	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
STA01	4	7	0	0	0	0	0	0	0		10	0	0	0	0	0	0	0	1
STA02	6	0	2	1	0	0	0	0	0		5	2	2	0	0	0	0	0	0
STA03	8	1	1	1	0	0	0	0	0		1	2	3	1	3	0	1	0	0
STA05	8	2	1	0	0	0	0	0	0		5	4	0	0	1	1	0	0	0
STA06	11	0	0	0	0	0	0	0	0		7	2	0	1	0	0	0	0	1
STA07	6	4	0	0	0	0	0	0	0		10	0	0	0	0	0	0	0	0
STA08	9	2	0	0	0	0	0	0	0		2	5	2	1	0	0	1	0	0
STA09	11	0	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
STA10	6	3	0	0	0	0	0	0	0		9	0	0	0	0	0	0	0	0
STA11	8	3	0	0	0	0	0	0	0		8	2	0	1	0	0	0	0	0
UMA02	1	9	1	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
UMA03	8	0	0	0	0	0	0	0	0		7	0	0	0	0	1	0	0	0
UMA04	8	1	0	0	0	1	0	0	0		10	0	0	0	0	0	0	0	0
UMA05	9	1	1	0	0	0	0	0	0		9	2	0	0	0	0	0	0	0
UMA06	10	0	0	0	0	0	0	0	0		10	0	0	0	0	0	0	0	0
UMA07	9	1	0	0	0	0	0	0	0		7	3	0	0	0	0	0	0	0
UMA08	10	1	0	0	0	0	0	0	0		11	0	0	0	0	0	0	0	0
UMA09	10	0	0	0	0	0	0	0	0		9	0	1	0	0	0	0	0	0
UMA10	10	1	0	0	0	0	0	0	0		8	1	2	0	0	0	0	0	1
UMA11	10	0	0	0	0	0	0	0	0		7	1	0	1	0	0	1	0	0
UNC02	11	0	0	0	0	0	0	0	0		10	0	1	0	0	0	0	0	0
UNC03	11	0	0	0	0	0	0	0	0		8	2	0	1	0	0	0	0	0
UNC04	7	3	0	1	0	0	0	0	0		9	2	0	0	0	0	0	0	0
UNC05	12	1	1	0	0	0	0	0	0		13	0	0	0	0	0	0	0	1
UNC06	11	0	0	0	0	0	0	0	0		9	1	0	0	0	0	0	1	0
UNC07	6	4	0	1	0	0	0	0	0		5	4	1	1	0	0	0	0	0
UNC08	9	2	0	0	0	0	0	0	0		9	2	0	0	0	0	0	0	0
UNC09	10	0	1	0	0	0	0	0	0		10	1	0	0	0	0	0	0	0
UNC10	11	0	0	0	0	0	0	0	0		6	2	1	1	1	0	0	0	0
Sum	340	59	8	4	1	1	0	0	0		321	49	16	9	5	4	3	1	5
% total	**79.3**	**13.8**	**1.9**	**0.9**	**0.2**	**0.2**	**0**	**0**	**0**		**74.8**	**11.4**	**3.7**	**2.1**	**1.2**	**0.9**	**0.7**	**0.2**	**1.2**



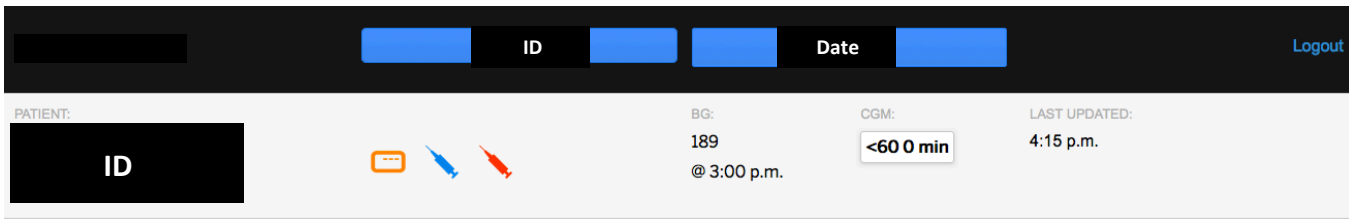


Figure S1. Schematic of the wearable bihormonal bionic pancreas system used in the outpatient study. Top: The control algorithm, which is written in C^{++} in an app that runs on an Apple iPhone 4S (station 2 – Control system), responds to CGM glucose levels streamed online every five minutes using the integrated G4 Platinum CGM (station 1 – Glucose measurement), and commands insulin and glucagon control doses using two t:slim infusion pumps (station 3 – Insulin and glucagon administration). Bottom: A screenshot (with subject-identifiable information redacted) from our web-based realtime remote-monitoring dashboard showing certain data fields from one of our experiments. The dashboard included live streaming of connection states between iPhone and CGM and iPhone and the pumps, as well as the current duration CGM glucose has been $<$3.3 mmol/l (shown in the screenshot as $<$60 mg/dl) and the last fingerstick blood glucose value (shown in the screenshot in units of mg/dl) that the user entered in the app on the iPhone.

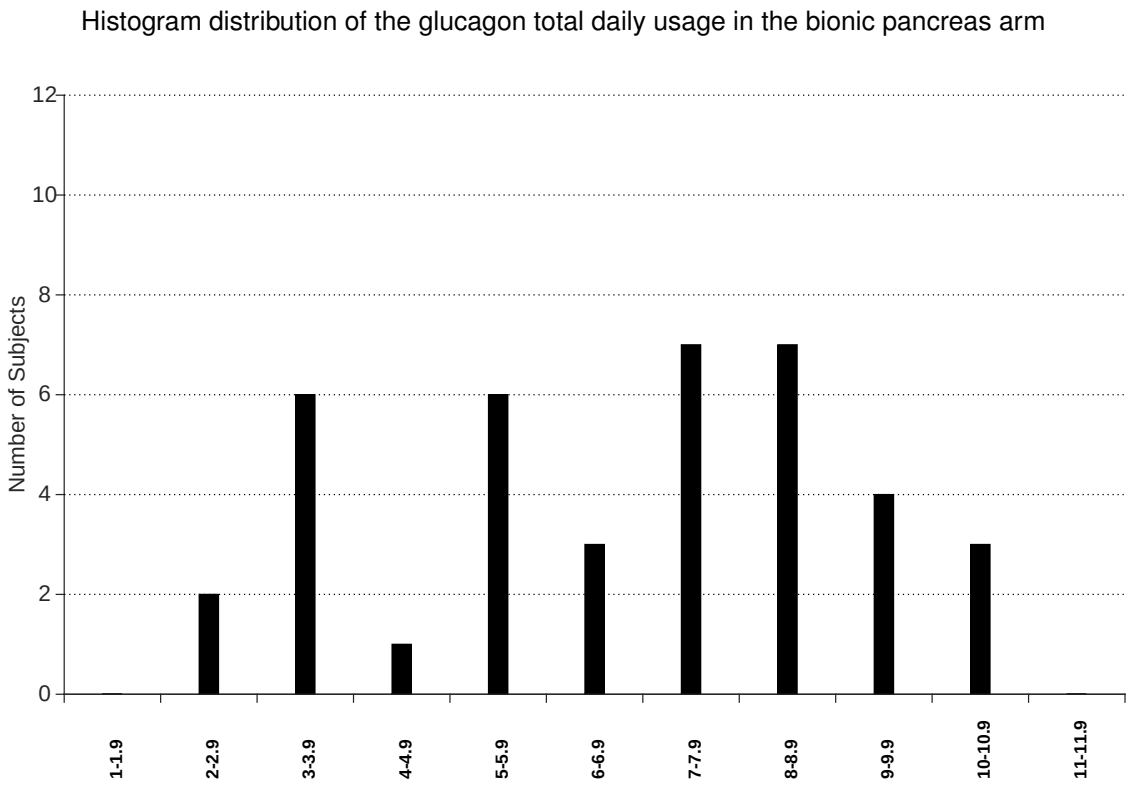


Figure S2. A histogram distribution of the glucagon total daily usage in the bionic pancreas arm, divided into intervals of 1 μg per kilogram of body mass per day.

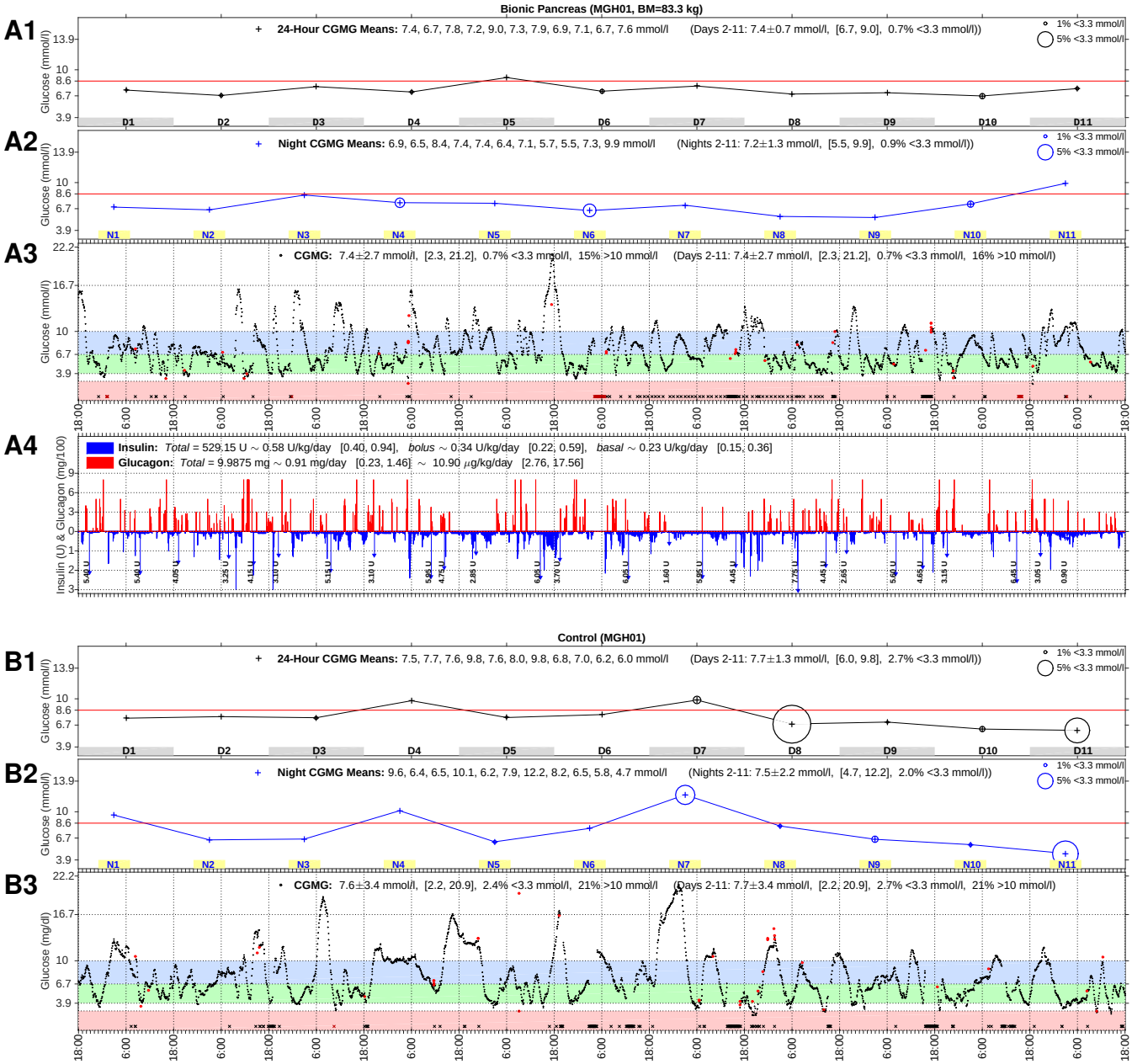


Figure S3. Outpatient experiments in subject #MGH01. Panels **A1–4** refer to results achieved by the BP and respectively show a plot of successive 24-hour average CGMG values and percentages of times CGMG $<$3.3 mmol/l, a plot of successive night-time CGMG average values and percentage of times CGMG $<$3.3 mmol/l, a plot of overall CGMG trace, and a plot of the corresponding insulin and glucagon doses (respectively as downward blue and upward red bars) automatically administered by the BP. Panels **B1–3** show results achieved in the comparator period, analogous to **A1–3**. Fingerstick PG is superimposed as red filled circles, with calibration PG indicated by magenta stars. Along the timeline, carbohydrate treatments for hypoglycemia are indicated by black rectangles, and meals and snacks by black triangles. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.4 mmol/l, mean of night time CGMG was 7.2 mmol/l, insulin–glucagon dosing was respectively 0.59 U/kg/day and 10.77 μg/kg/day, CGMG was $<$3.3 mmol/l 0.7% of the time (0.9% at night) and $>$10 mmol/l 16% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.7 mmol/l, mean of night time CGMG was 7.4 mmol/l, CGMG was $<$3.3 mmol/l 2.7% of the time (2.0% at night), and $>$10 mmol/l 21% of the time. Symptoms of hypoglycemia were reported 15 times during the BP period and 14 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 9 times during the BP period and 12 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/3/1 during the BP period, and 0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

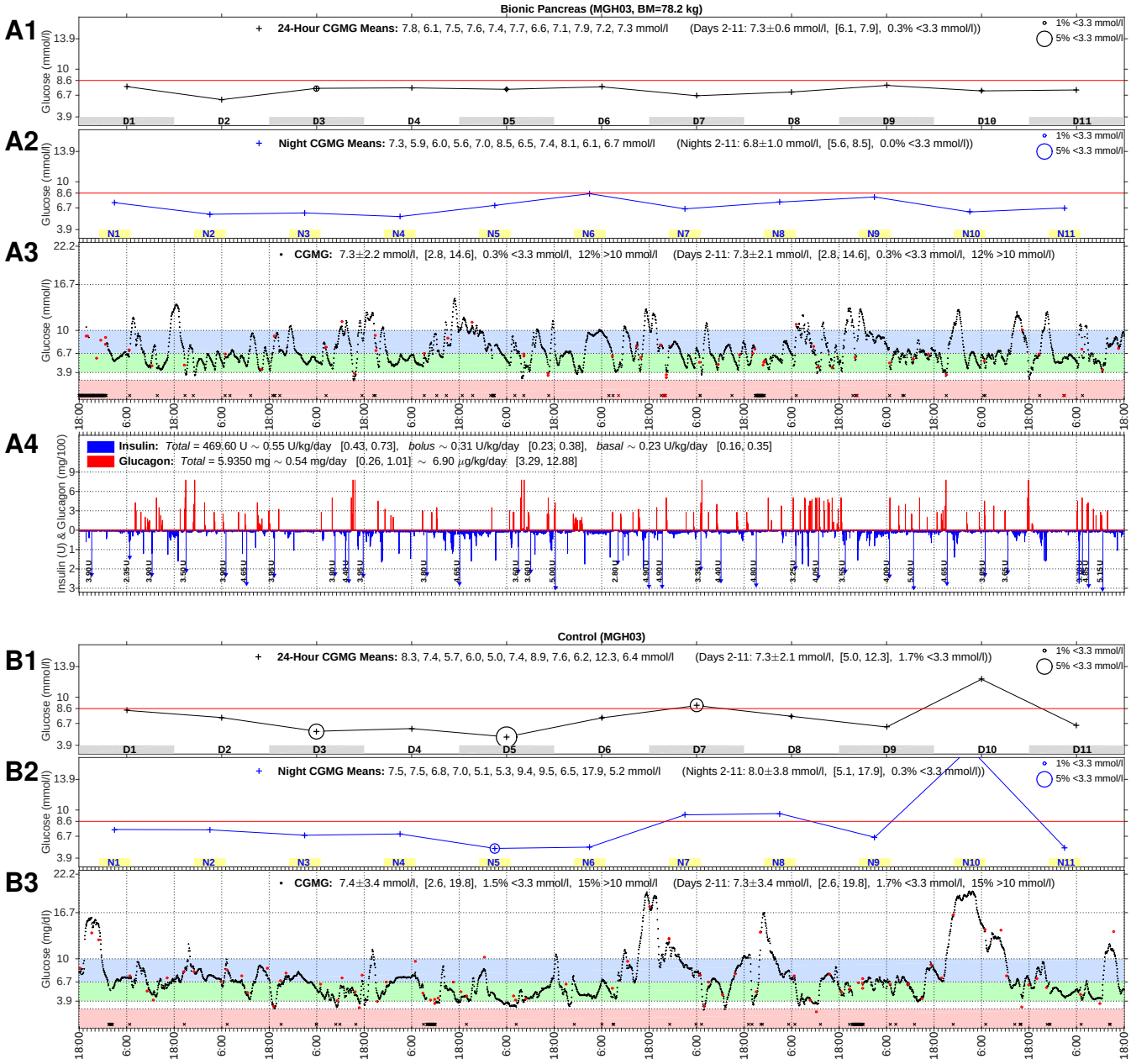


Figure S4. Outpatient experiments in subject #MGH03. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.3 mmol/l, mean of night time CGMG was 6.8 mmol/l, insulin–glucagon dosing was respectively 0.56 U/kg/day and 7.15 μg/kg/day, CGMG was $<$3.3 mmol/l 0.3% of the time (0% at night) and $>$10 mmol/l 12% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.3 mmol/l, mean of night time CGMG was 8.1 mmol/l, CGMG was $<$3.3 mmol/l 1.7% of the time (0.2% at night), and $>$10 mmol/l 15% of the time. Symptoms of hypoglycemia were reported twice during the BP period and 9 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported once during the BP period and 10 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

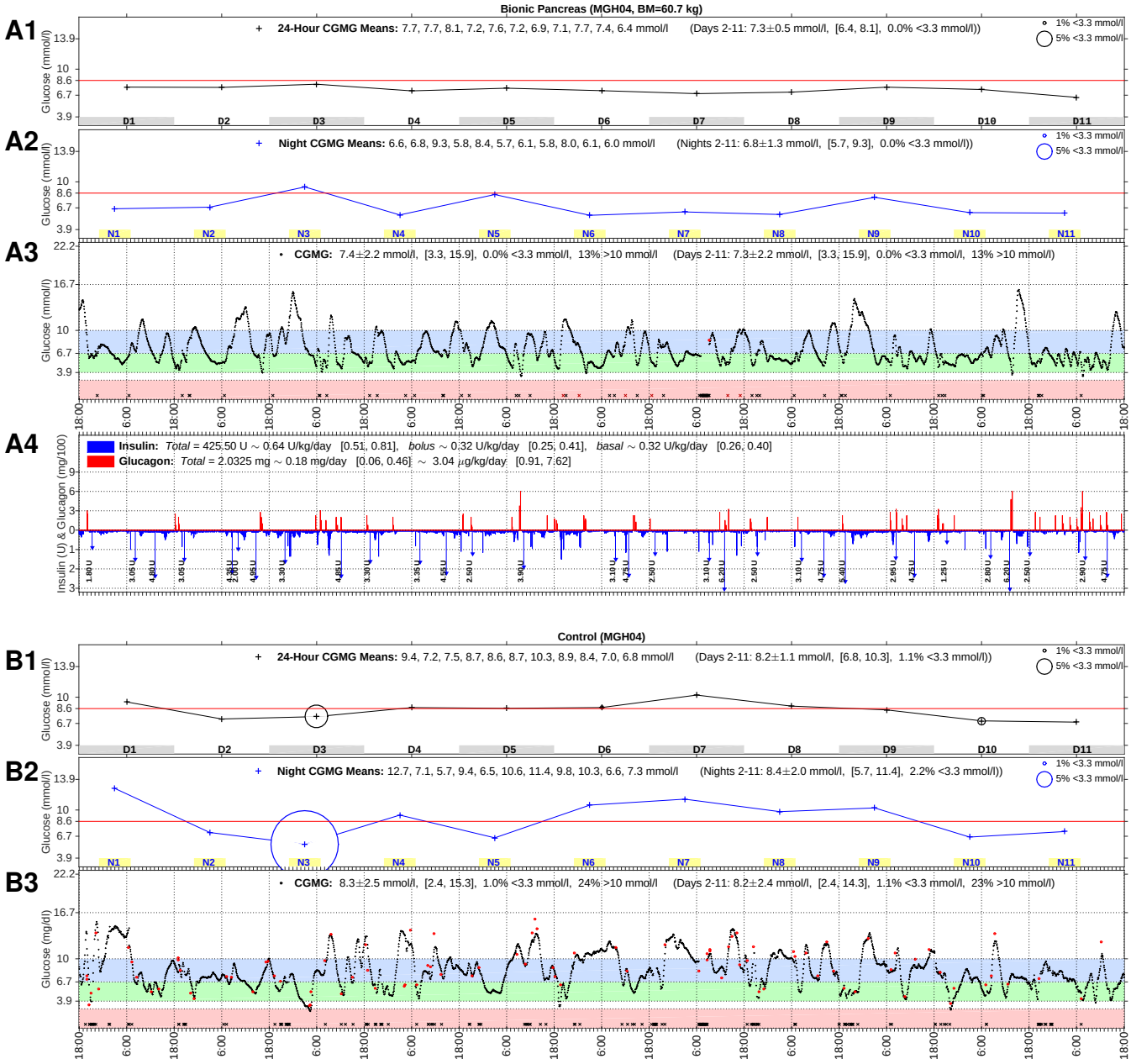


Figure S5. Outpatient experiments in subject #MGH04. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.6 mmol/l, mean of night time CGMG was 7.4 mmol/l, insulin–glucagon dosing was respectively 0.64 U/kg/day and 3.90 μg/kg/day, CGMG was $<$3.3 mmol/l 0.2% of the time (0% at night) and $>$10 mmol/l 15% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.7 mmol/l, mean of night time CGMG was 7.9 mmol/l, CGMG was $<$3.3 mmol/l 0.7% of the time (0.6% at night), and $>$10 mmol/l 18% of the time. Symptoms of hypoglycemia were reported 3 times during the BP period and 7 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 3 times during the BP period and 8 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

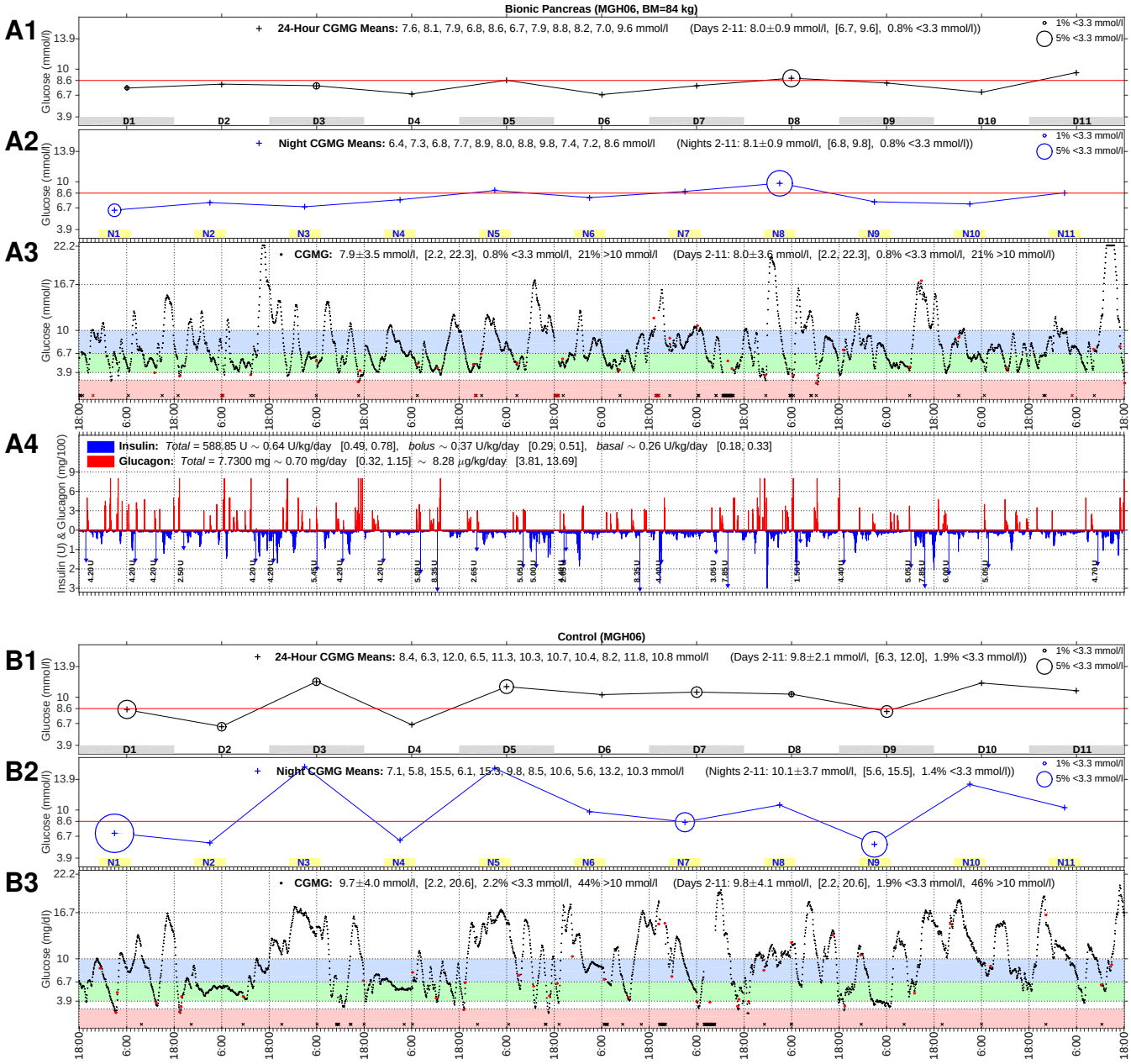


Figure S6. Outpatient experiments in subject #MGH06. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.9 mmol/l, mean of night time CGMG was 8.1 mmol/l, insulin–glucagon dosing was respectively 0.65 U/kg/day and 7.91 μg/kg/day, CGMG was $<$3.3 mmol/l 0.8% of the time (0.8% at night) and $>$10 mmol/l 21% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.8 mmol/l, mean of night time CGMG was 10.1 mmol/l, CGMG was $<$3.3 mmol/l 1.9% of the time (1.4% at night), and $>$10 mmol/l 46% of the time. Symptoms of hypoglycemia were reported 14 times during the BP period and 20 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 6 times during the BP period and 20 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/2/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

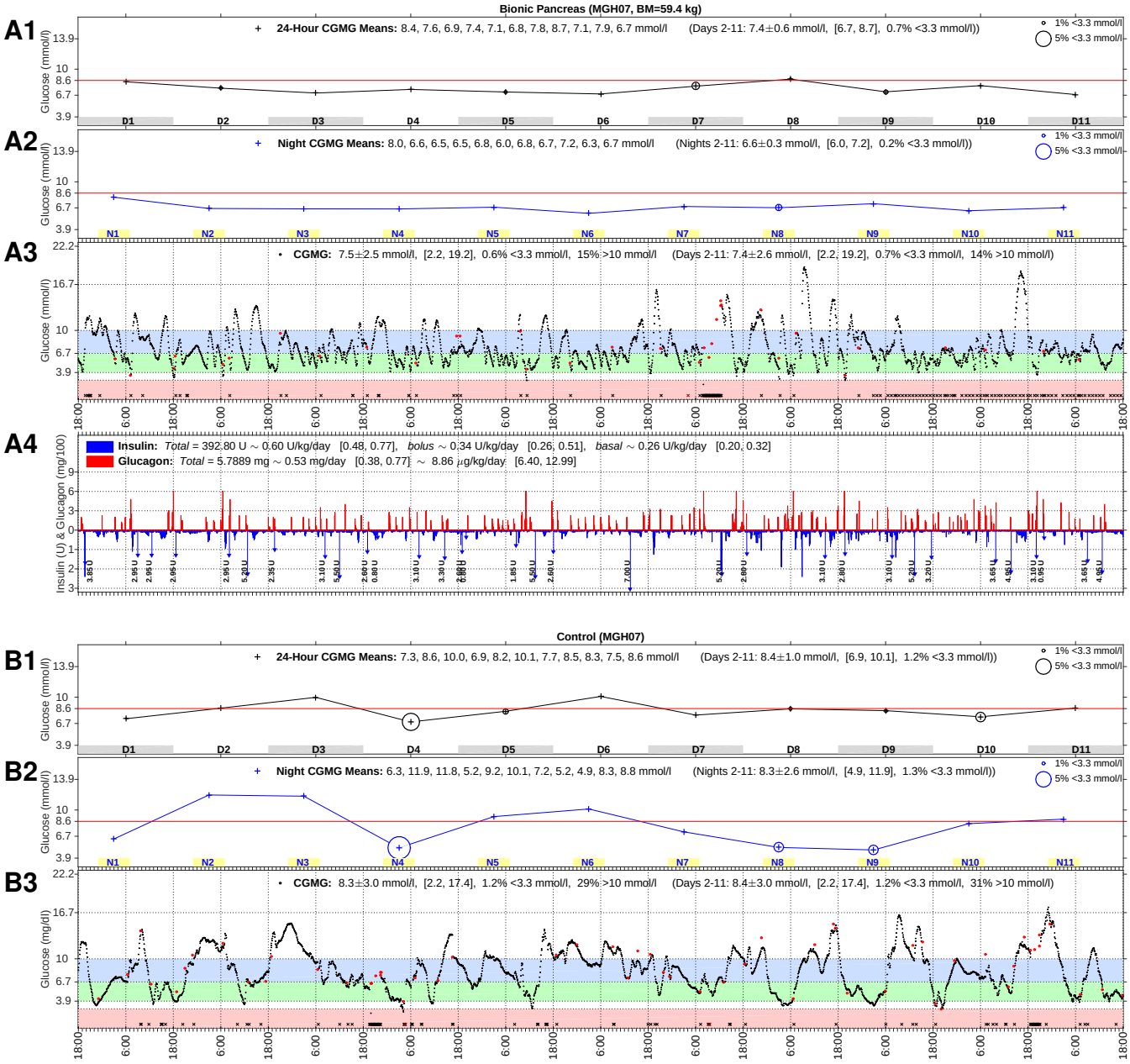


Figure S7. Outpatient experiments in subject #MGH07. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.4 mmol/l, mean of night time CGMG was 6.6 mmol/l, insulin–glucagon dosing was respectively 0.59 U/kg/day and 8.92 μg/kg/day, CGMG was $<$3.3 mmol/l 0.7% of the time (0.2% at night) and $>$10 mmol/l 14% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.4 mmol/l, mean of night time CGMG was 8.3 mmol/l, CGMG was $<$3.3 mmol/l 1.2% of the time (1.4% at night), and $>$10 mmol/l 31% of the time. Symptoms of hypoglycemia were reported 7 times during the BP period and 5 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported twice during the BP period and 5 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/1/0/0/2/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

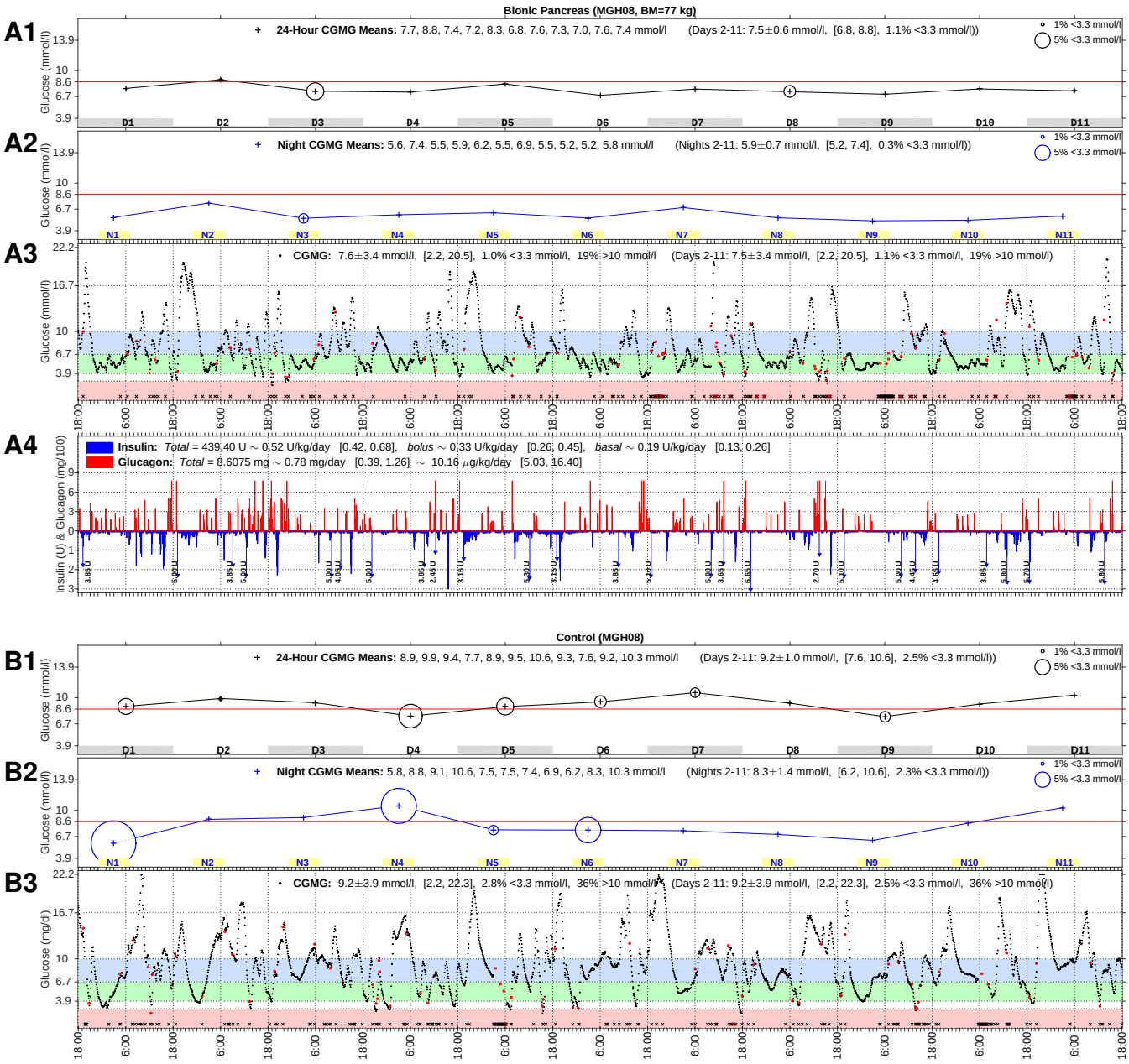


Figure S8. Outpatient experiments in subject #MGH08. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.6 mmol/l, mean of night time CGMG was 5.9 mmol/l, insulin–glucagon dosing was respectively 0.51 U/kg/day and 9.98 μg/kg/day, CGMG was $<$3.3 mmol/l 1.1% of the time (0.3% at night) and $>$10 mmol/l 19% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.2 mmol/l, mean of night time CGMG was 8.3 mmol/l, CGMG was $<$3.3 mmol/l 2.5% of the time (2.2% at night), and $>$10 mmol/l 36% of the time. Symptoms of hypoglycemia were reported 19 times during the BP period and 18 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 6 times during the BP period and 18 times during the comparator period. Daily nausea scores on a scale of 0–10 were 3/0/0/0/0/0/0/0/2/0 during the BP period, and 0/0/0/0/0/0/0/0/3/2/0 during the comparator period. The subject reported no vomiting during the BP period and 1 episode of vomiting during the comparator period after treatment of a low blood sugar, and believed it to be related to her history of gastric bypass surgery.

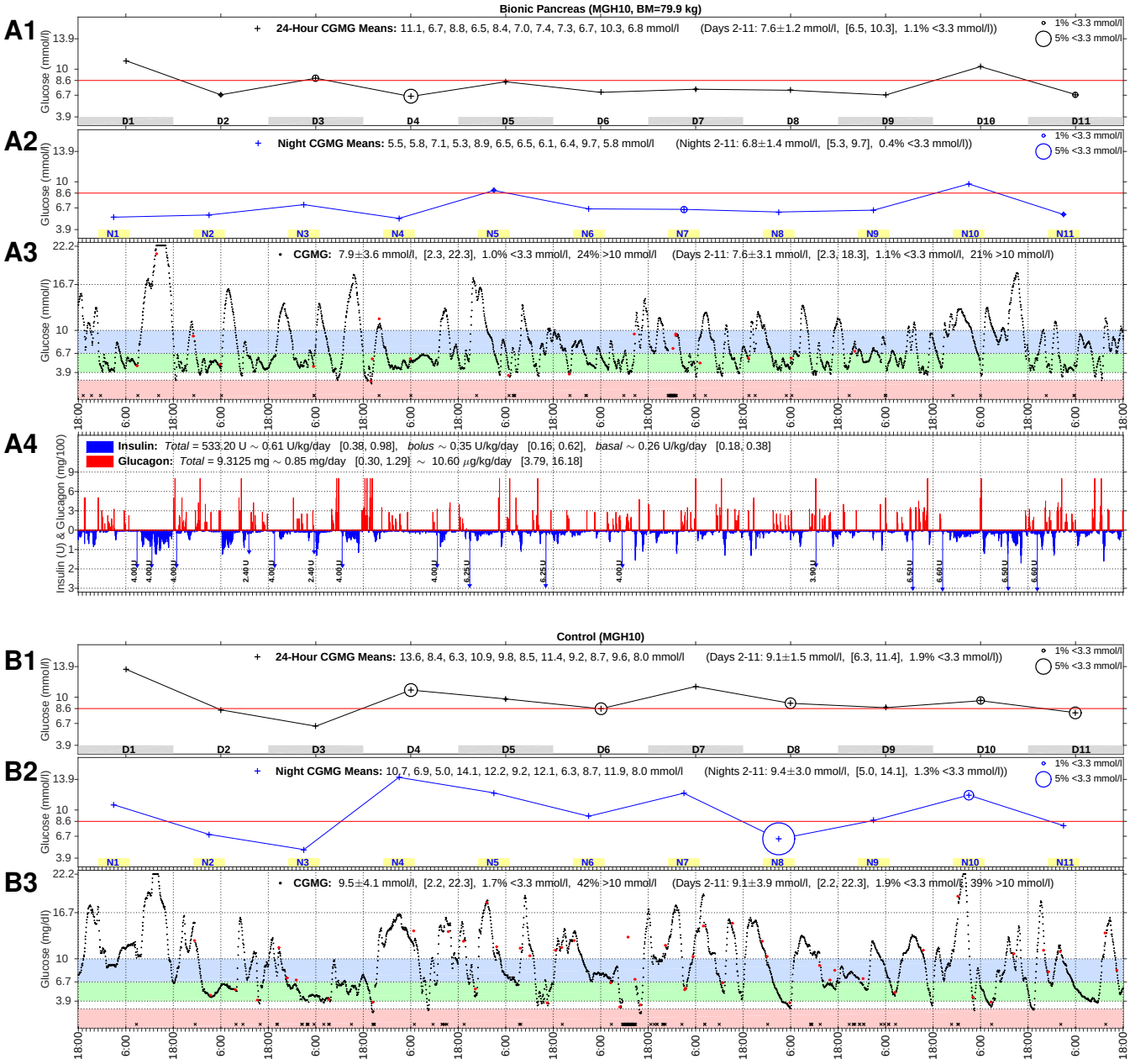


Figure S9. Outpatient experiments in subject #MGH10. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.6 mmol/l, mean of night time CGMG was 6.8 mmol/l, insulin–glucagon dosing was respectively 0.57 U/kg/day and 10.96 μg/kg/day, CGMG was $<$3.3 mmol/l 1.1% of the time (0.3% at night) and $>$10 mmol/l 22% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.1 mmol/l, mean of night time CGMG was 9.4 mmol/l, CGMG was $<$3.3 mmol/l 1.9% of the time (1.4% at night), and $>$10 mmol/l 39% of the time. Symptoms of hypoglycemia were reported twice during the BP period and 4 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported twice during the BP period and 4 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

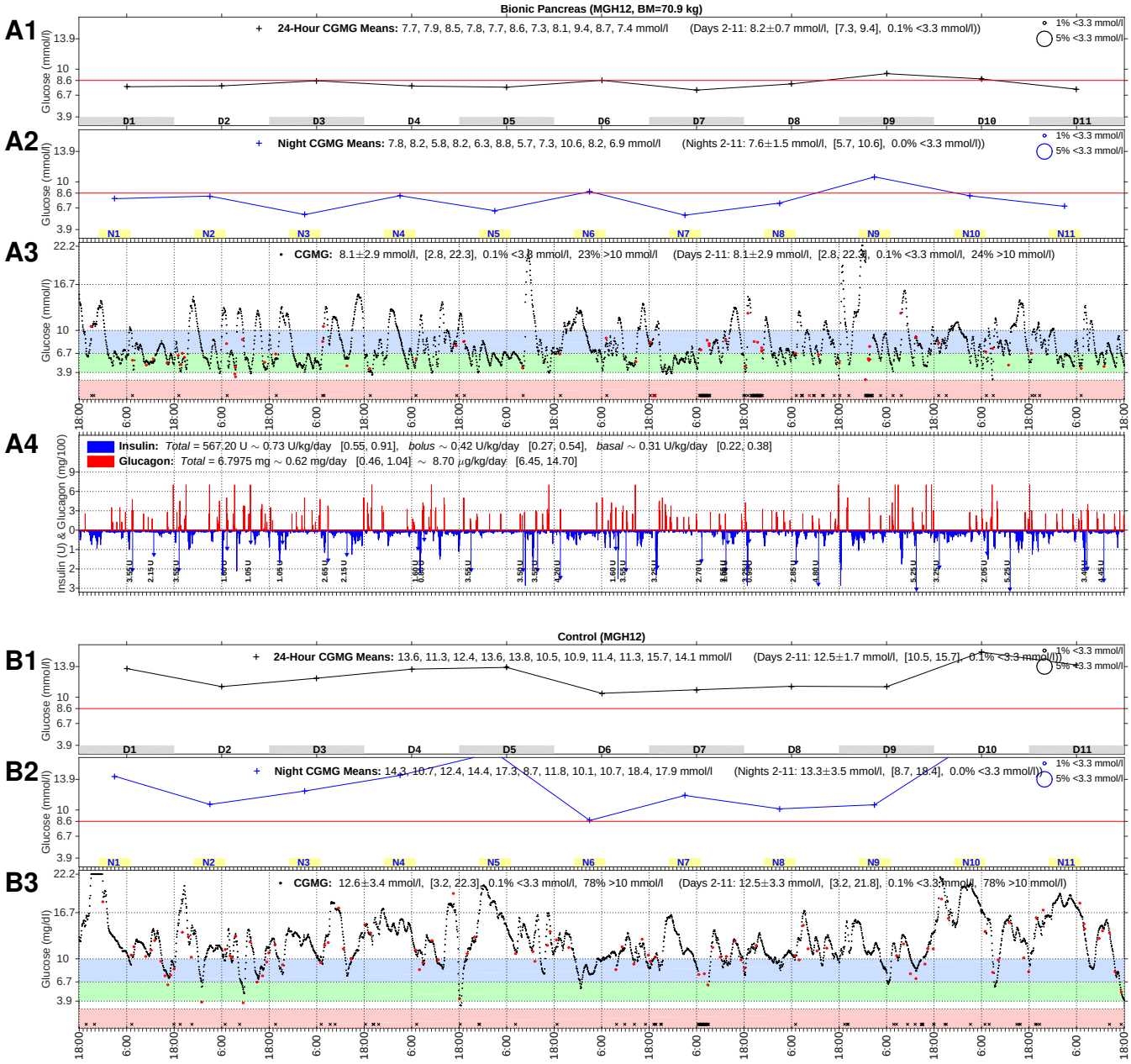


Figure S10. Outpatient experiments in subject #MGH12. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.2 mmol/l, mean of night time CGMG was 7.6 mmol/l, insulin–glucagon dosing was respectively 0.74 U/kg/day and 8.94 μg/kg/day, CGMG was $<$3.3 mmol/l 0.1% of the time (0% at night) and $>$10 mmol/l 24% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 12.5 mmol/l, mean of night time CGMG was 13.3 mmol/l, CGMG was $<$3.3 mmol/l 0.1% of the time (0% at night), and $>$10 mmol/l 78% of the time. Symptoms of hypoglycemia were reported 14 times during the BP period and twice during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 9 times during the BP period and twice during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

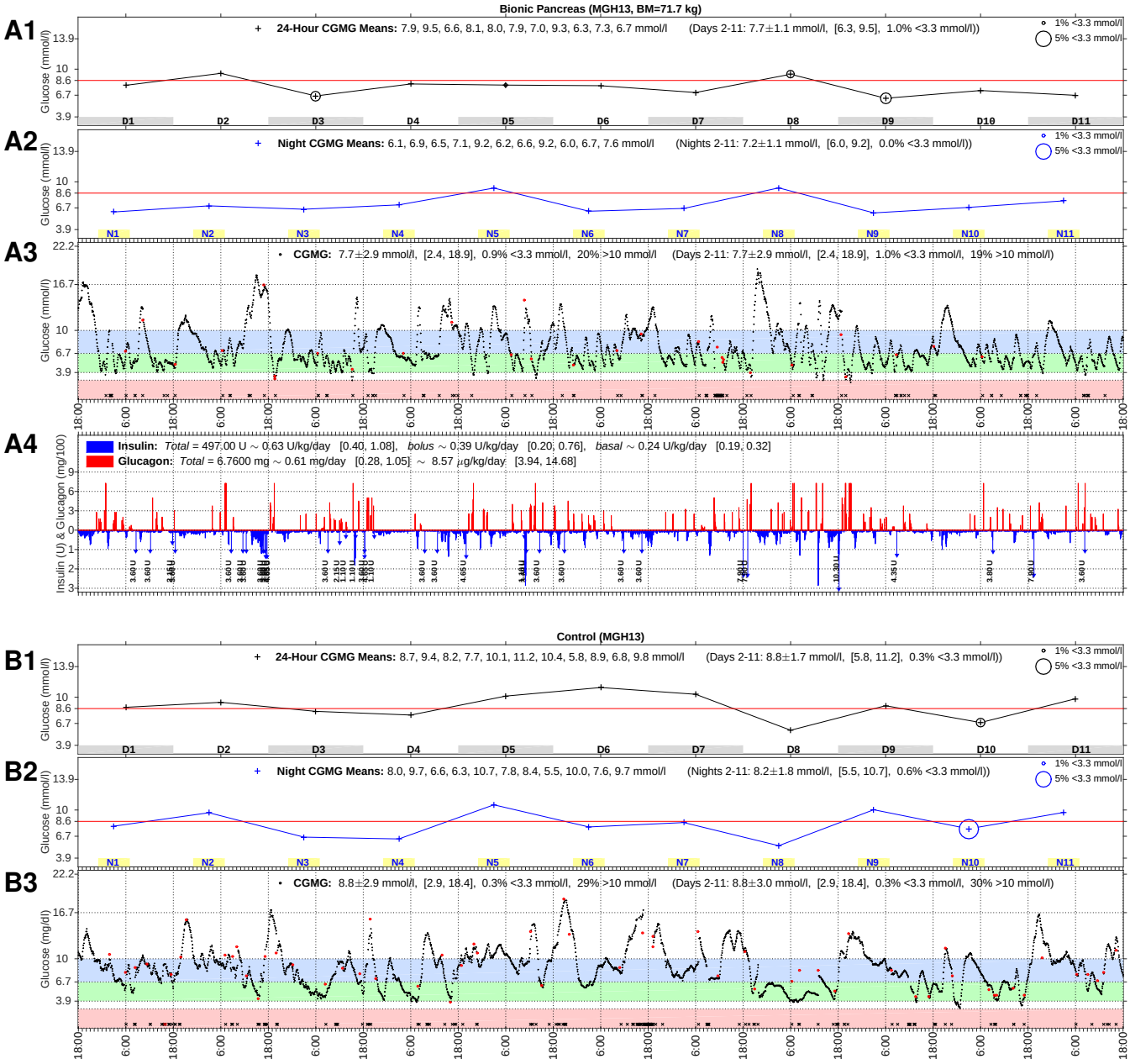


Figure S11. Outpatient experiments in subject #MGH13. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.7 mmol/l, mean of night time CGMG was 7.2 mmol/l, insulin–glucagon dosing was respectively 0.64 U/kg/day and 8.48 μg/kg/day, CGMG was $<$3.3 mmol/l 1.0% of the time (0% at night) and $>$10 mmol/l 19% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.8 mmol/l, mean of night time CGMG was 8.2 mmol/l, CGMG was $<$3.3 mmol/l 0.3% of the time (0.6% at night), and $>$10 mmol/l 30% of the time. Symptoms of hypoglycemia were reported 27 times during the BP period and 3 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 14 times during the BP period and 3 times during the comparator period. Daily nausea scores on a scale of 0–10 were 1/8/2/1/3/2/1/1/1/1/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

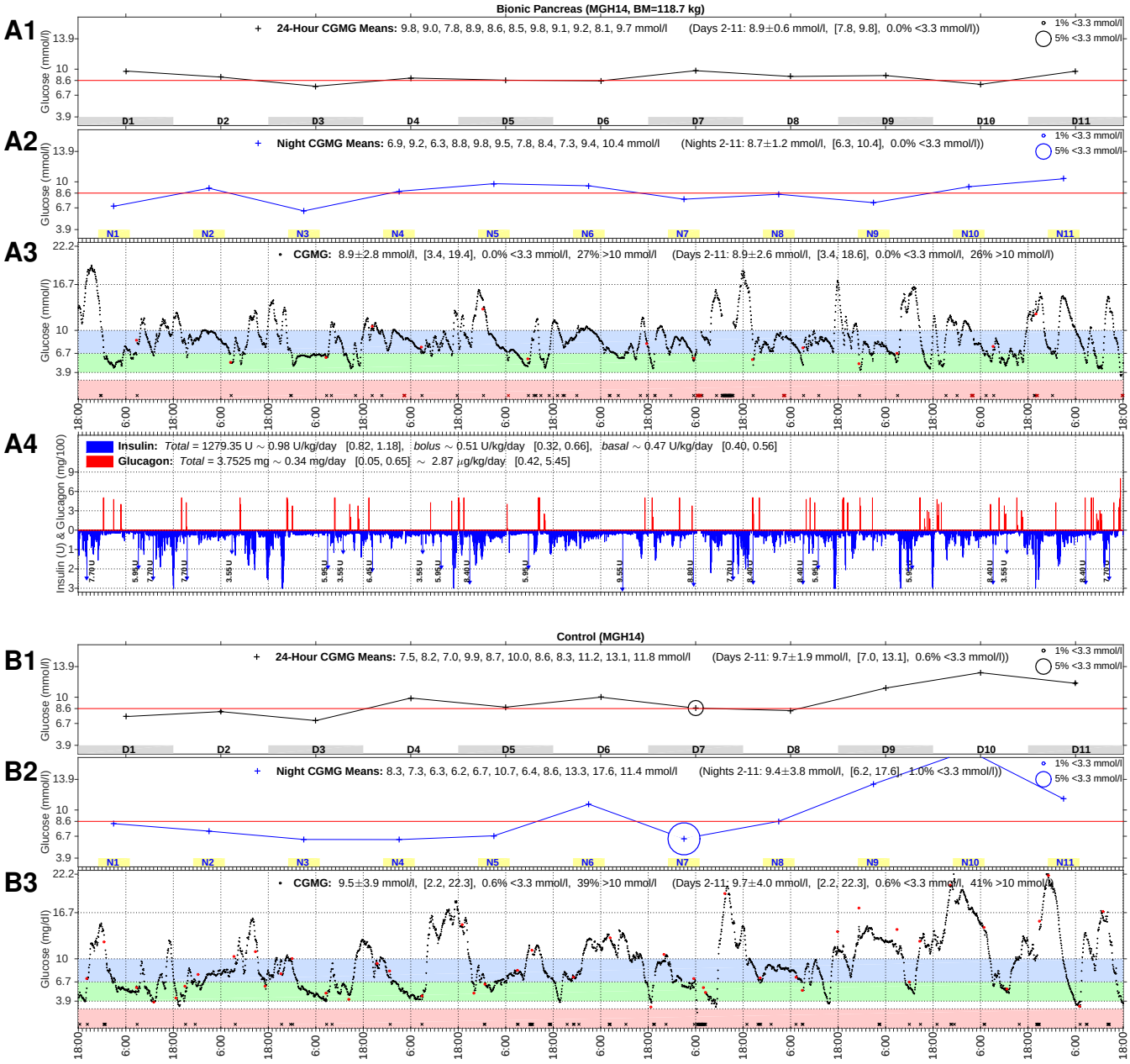


Figure S12. Outpatient experiments in subject #MGH14. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.8 mmol/l, mean of night time CGMG was 8.7 mmol/l, insulin–glucagon dosing was respectively 0.97 U/kg/day and 2.99 μg/kg/day, CGMG was $<$3.3 mmol/l 0% of the time (0% at night) and $>$10 mmol/l 26% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.7 mmol/l, mean of night time CGMG was 9.4 mmol/l, CGMG was $<$3.3 mmol/l 0.6% of the time (0.9% at night), and $>$10 mmol/l 41% of the time. Symptoms of hypoglycemia were reported 4 times during the BP period and 4 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 4 times during the BP period and 4 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

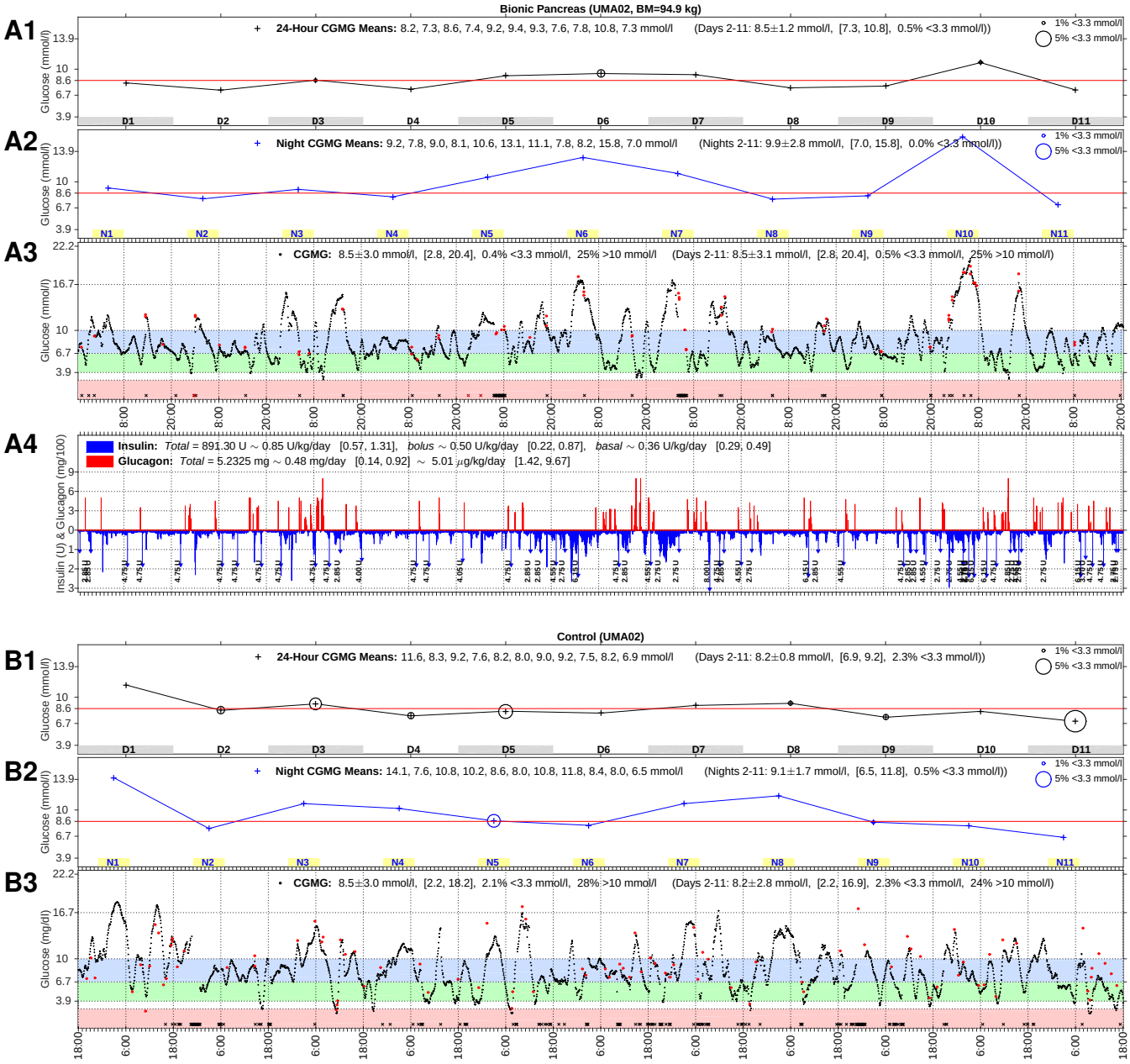


Figure S13. Outpatient experiments in subject #UMA02. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.5 mmol/l, mean of night time CGMG was 9.9 mmol/l, insulin–glucagon dosing was respectively 0.88 U/kg/day and 5.37 μg/kg/day, CGMG was $<$3.3 mmol/l 0.5% of the time (0% at night) and $>$10 mmol/l 25% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.2 mmol/l, mean of night time CGMG was 9.1 mmol/l, CGMG was $<$3.3 mmol/l 2.3% of the time (0.4% at night), and $>$10 mmol/l 24% of the time. Symptoms of hypoglycemia were reported twice during the BP period and 10 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported twice during the BP period and 10 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

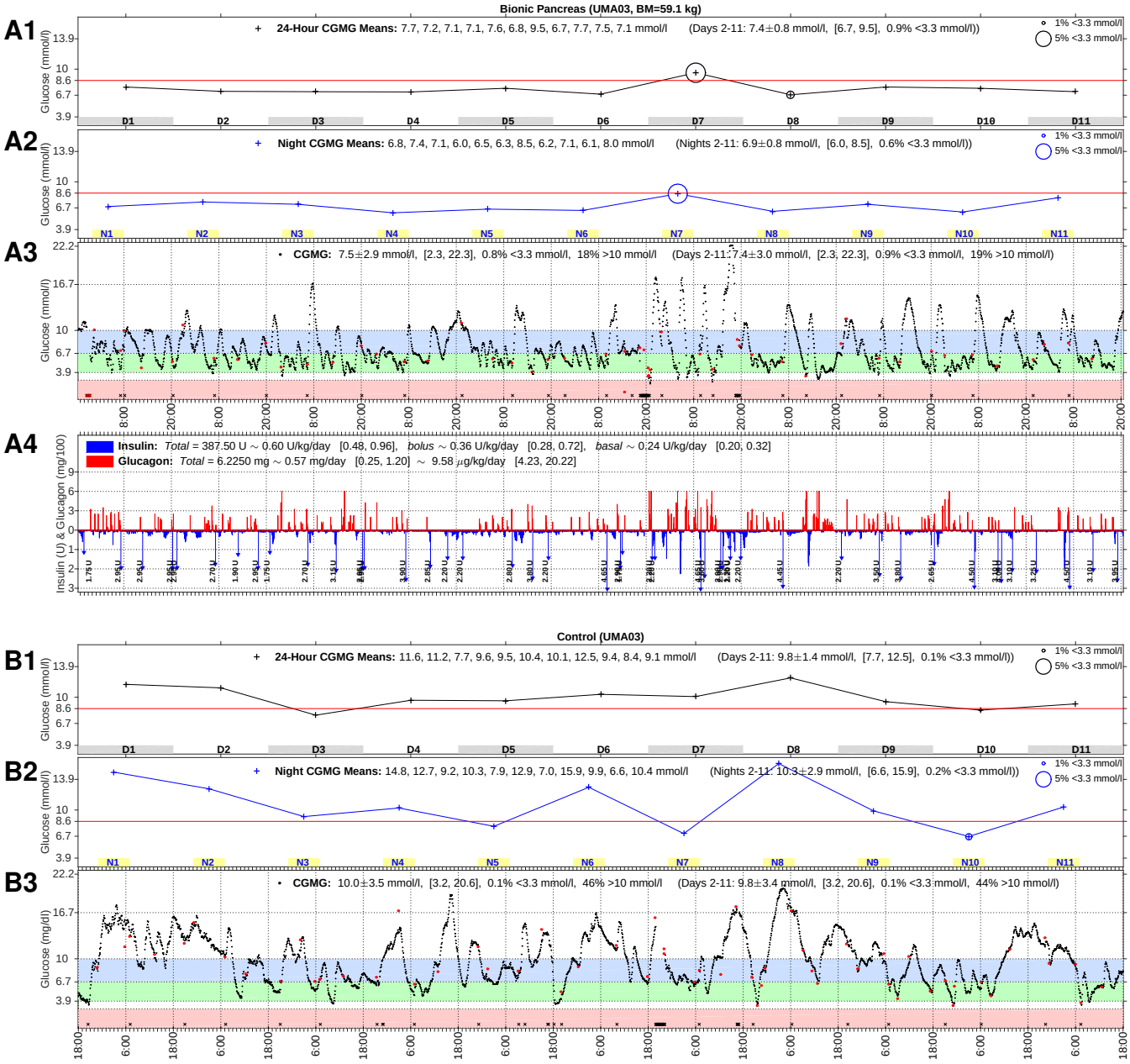


Figure S14. Outpatient experiments in subject #UMA03. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.4 mmol/l, mean of night time CGMG was 6.9 mmol/l, insulin–glucagon dosing was respectively 0.60 U/kg/day and 9.68 μg/kg/day, CGMG was $<$3.3 mmol/l 0.9% of the time (0.6% at night) and $>$10 mmol/l 19% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.8 mmol/l, mean of night time CGMG was 10.3 mmol/l, CGMG was $<$3.3 mmol/l 0.1% of the time (0.2% at night), and $>$10 mmol/l 44% of the time. Symptoms of hypoglycemia were reported once during the BP period and 4 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and 4 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

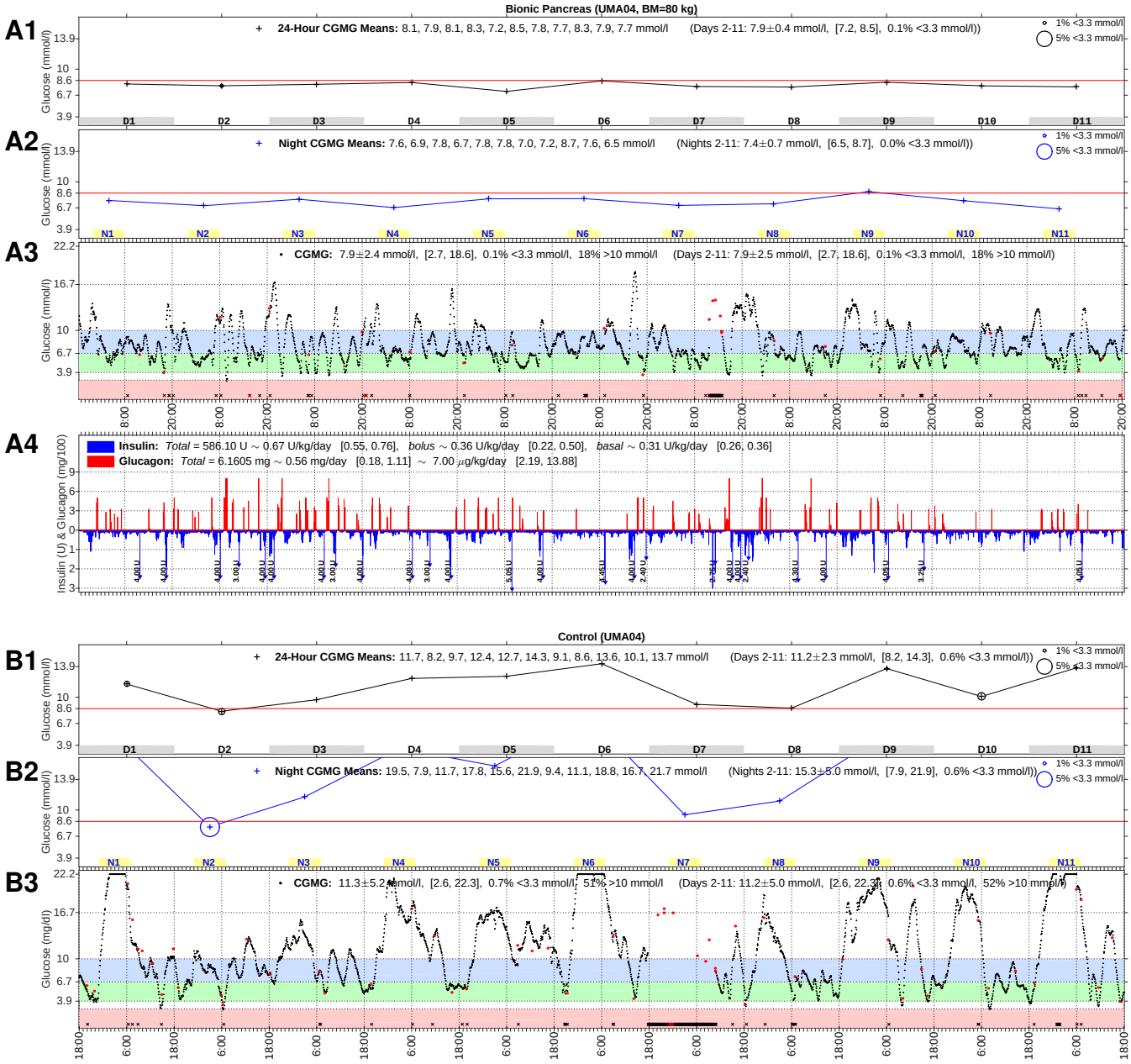


Figure S15. Outpatient experiments in subject #UMA04. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.9 mmol/l, mean of night time CGMG was 7.4 mmol/l, insulin–glucagon dosing was respectively 0.67 U/kg/day and 7.06 μg/kg/day, CGMG was $<$3.3 mmol/l 0.1% of the time (0% at night) and $>$10 mmol/l 18% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 11.2 mmol/l, mean of night time CGMG was 15.3 mmol/l, CGMG was $<$3.3 mmol/l 0.6% of the time (0.6% at night), and $>$10 mmol/l 52% of the time. Symptoms of hypoglycemia were reported 4 times during the BP period and 8 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported once during the BP period and 5 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/5/3/0/0/0/0/0/8/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

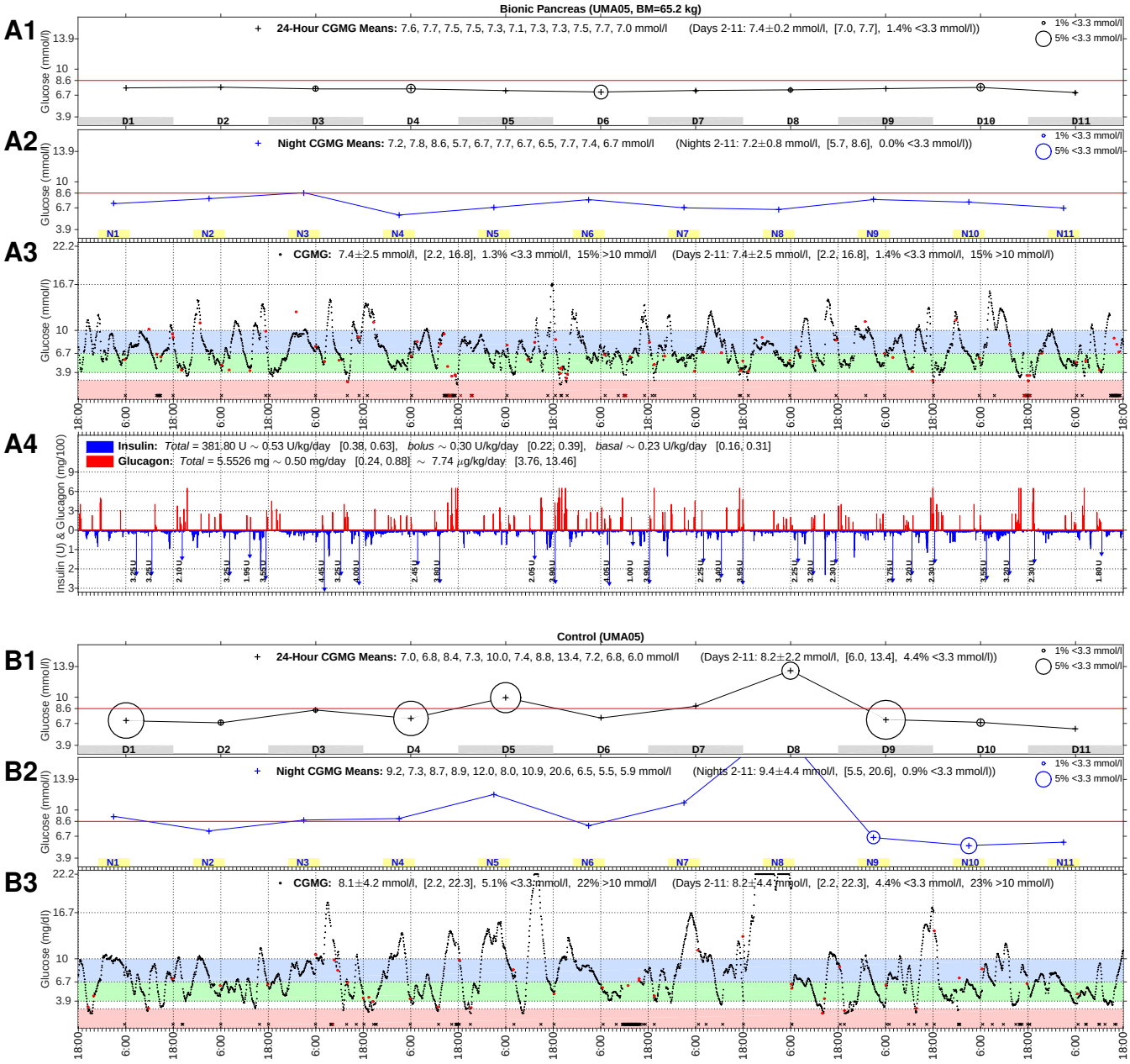


Figure S16. Outpatient experiments in subject #UMA05. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.4 mmol/l, mean of night time CGMG was 7.2 mmol/l, insulin–glucagon dosing was respectively 0.54 U/kg/day and 7.98 μg/kg/day, CGMG was $<$3.3 mmol/l 1.4% of the time (0% at night) and $>$10 mmol/l 15% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.2 mmol/l, mean of night time CGMG was 9.4 mmol/l, CGMG was $<$3.3 mmol/l 4.4% of the time (0.9% at night), and $>$10 mmol/l 23% of the time. Symptoms of hypoglycemia were reported 7 times during the BP period and 21 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 7 times during the BP period and 21 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

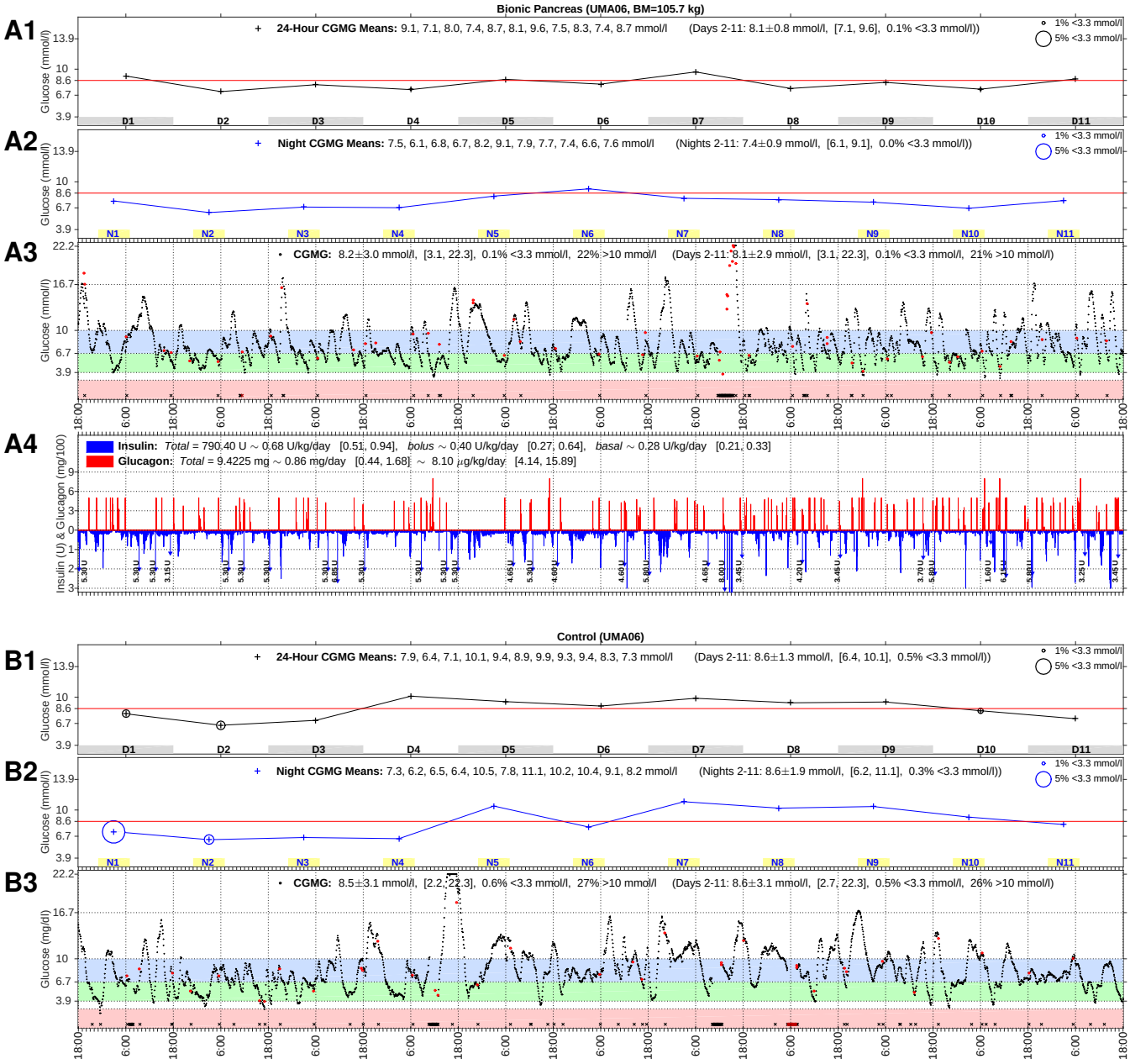


Figure S17. Outpatient experiments in subject #UMA06. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.1 mmol/l, mean of night time CGMG was 7.4 mmol/l, insulin–glucagon dosing was respectively 0.67 U/kg/day and 8.37 μg/kg/day, CGMG was $<$3.3 mmol/l 0.1% of the time (0% at night) and $>$10 mmol/l 21% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.6 mmol/l, mean of night time CGMG was 8.6 mmol/l, CGMG was $<$3.3 mmol/l 0.5% of the time (0.3% at night), and $>$10 mmol/l 27% of the time. Symptoms of hypoglycemia were reported 6 times during the BP period and 8 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported twice during the BP period and 8 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

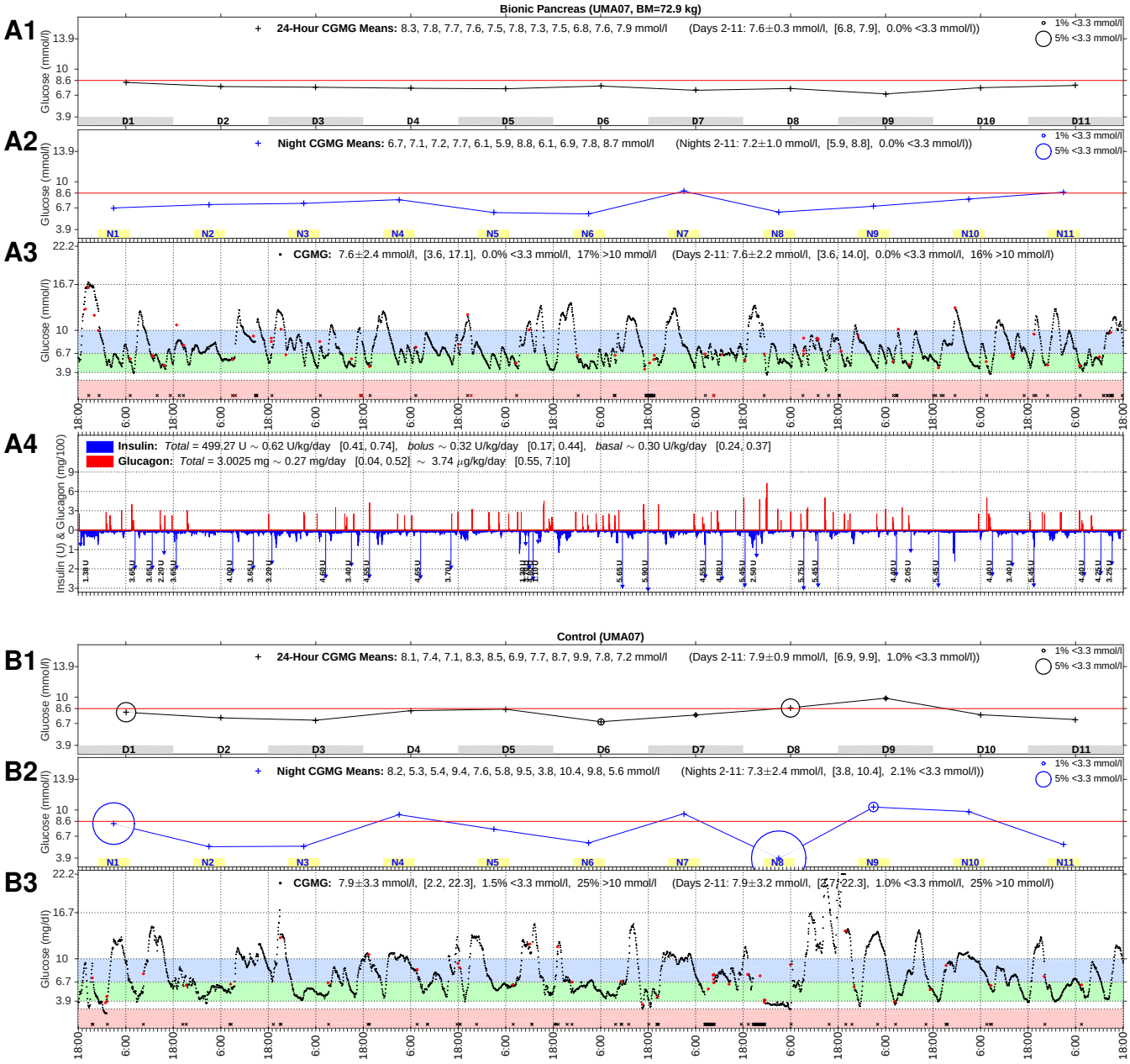


Figure S18. Outpatient experiments in subject #UMA07. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.6 mmol/l, mean of night time CGMG was 7.2 mmol/l, insulin–glucagon dosing was respectively 0.62 U/kg/day and 3.68 μg/kg/day, CGMG was $<$3.3 mmol/l 0% of the time (0% at night) and $>$10 mmol/l 16% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.9 mmol/l, mean of night time CGMG was 7.3 mmol/l, CGMG was $<$3.3 mmol/l 1.0% of the time (2.1% at night), and $>$10 mmol/l 25% of the time. Symptoms of hypoglycemia were reported as not occurring during the BP period and 6 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and 6 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

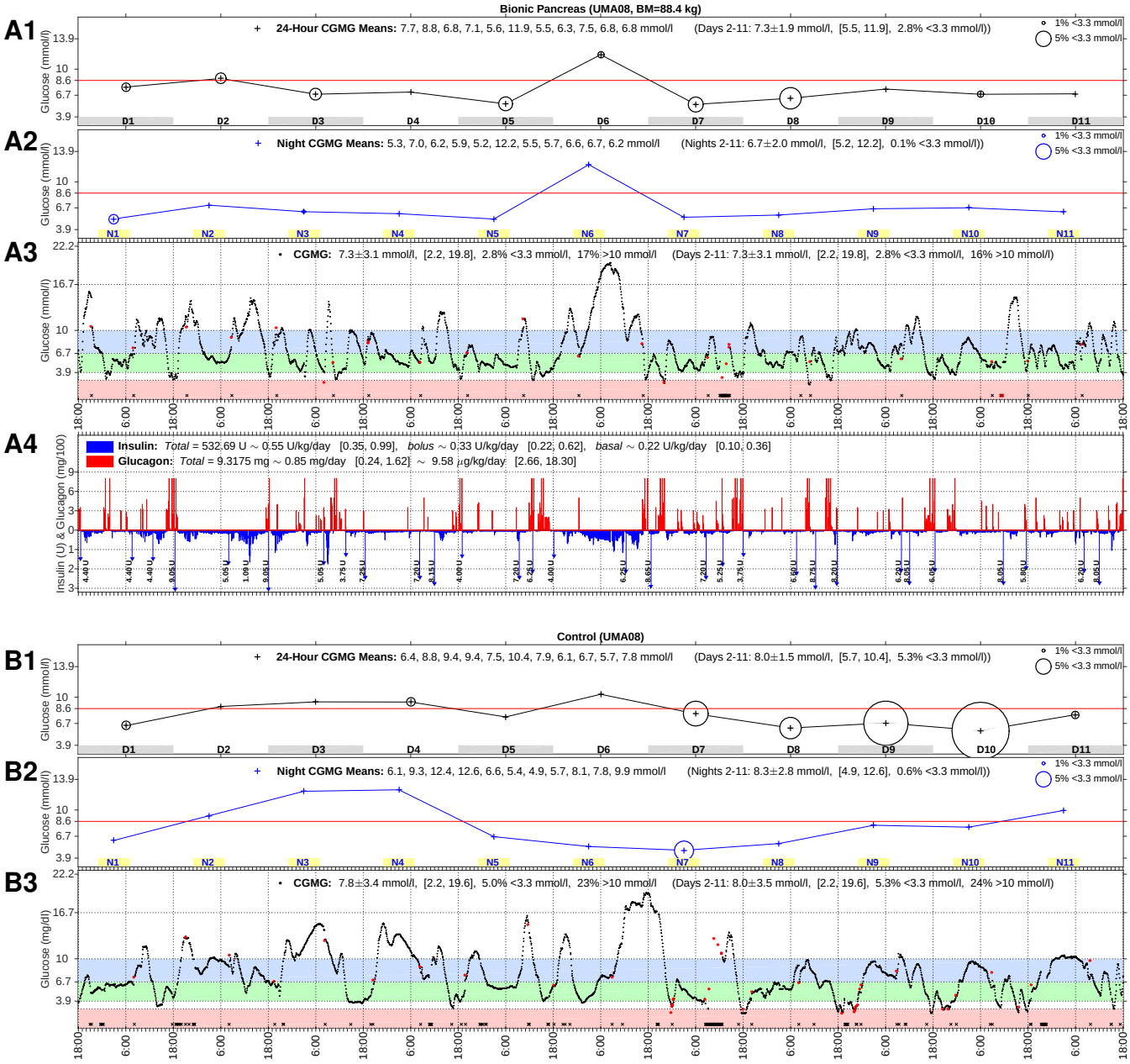


Figure S19. Outpatient experiments in subject #UMA08. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.3 mmol/l, mean of night time CGMG was 6.7 mmol/l, insulin–glucagon dosing was respectively 0.55 U/kg/day and 9.26 μg/kg/day, CGMG was $<$3.3 mmol/l 2.8% of the time (0.1% at night) and $>$10 mmol/l 16% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.9 mmol/l, mean of night time CGMG was 8.3 mmol/l, CGMG was $<$3.3 mmol/l 5.3% of the time (0.6% at night), and $>$10 mmol/l 24% of the time. Symptoms of hypoglycemia were reported 6 times during the BP period and 8 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 3 times during the BP period and 9 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/3/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

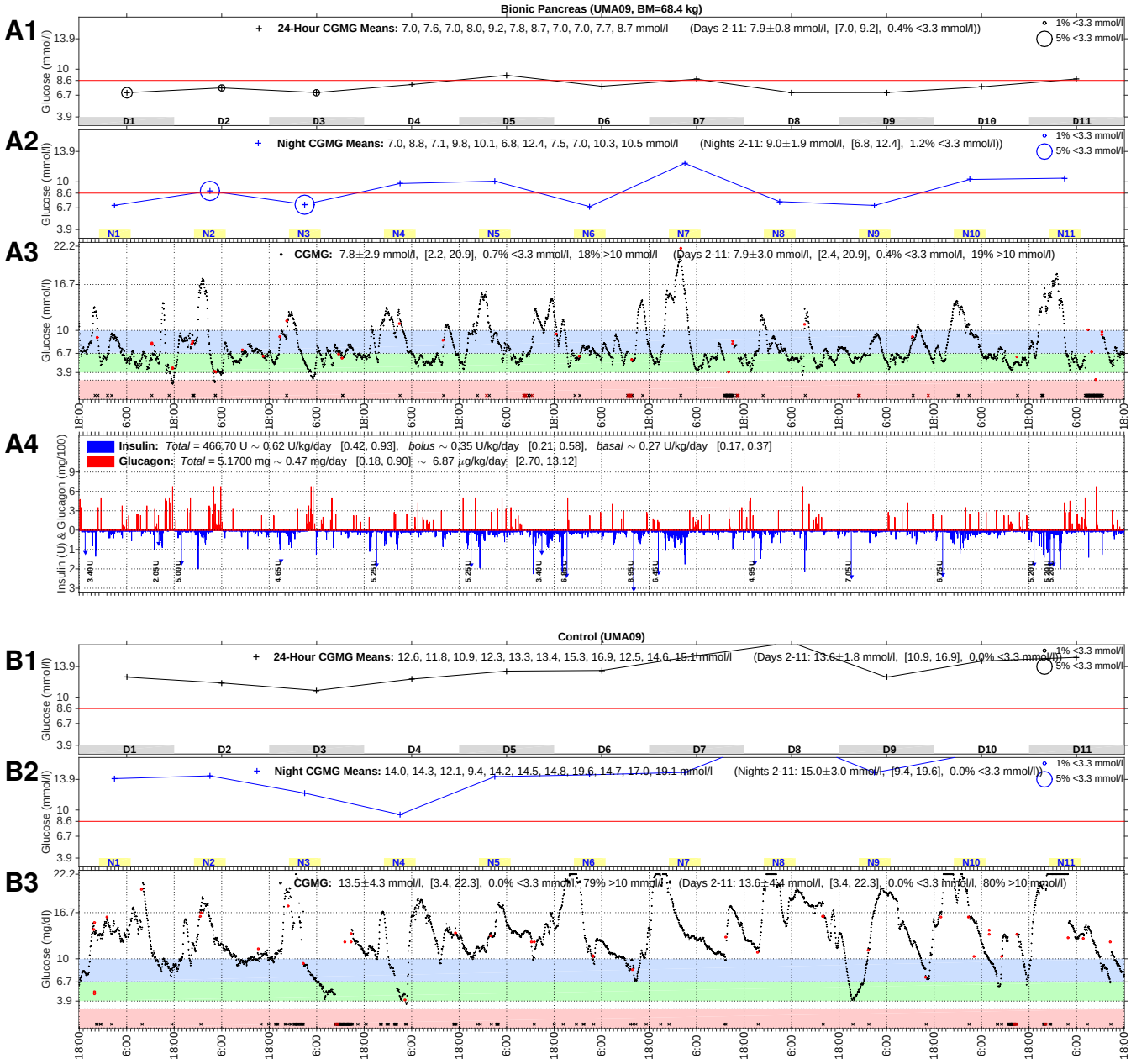


Figure S20. Outpatient experiments in subject #UMA09. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.9 mmol/l, mean of night time CGMG was 9.1 mmol/l, insulin–glucagon dosing was respectively 0.64 U/kg/day and 6.25 μg/kg/day, CGMG was $<$3.3 mmol/l 0.4% of the time (1.2% at night) and $>$10 mmol/l 19% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 13.6 mmol/l, mean of night time CGMG was 15.0 mmol/l, CGMG was $<$3.3 mmol/l 0% of the time (0% at night), and $>$10 mmol/l 80% of the time. Symptoms of hypoglycemia were reported as not occurring during the BP period and the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

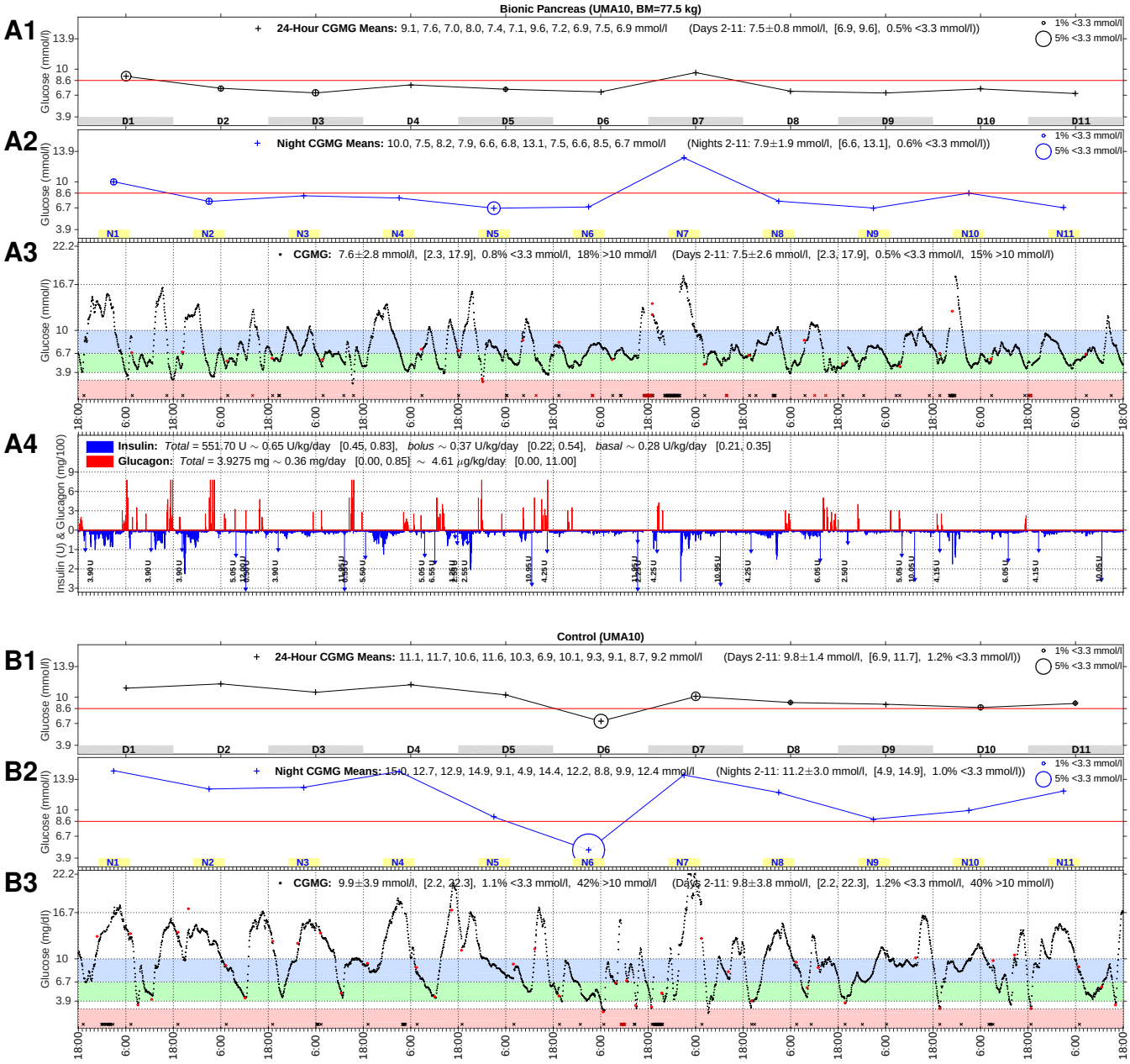


Figure S21. Outpatient experiments in subject #UMA10. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.5 mmol/l, mean of night time CGMG was 7.9 mmol/l, insulin–glucagon dosing was respectively 0.63 U/kg/day and 3.97 μg/kg/day, CGMG was $<$3.3 mmol/l 0.5% of the time (0.6% at night) and $>$10 mmol/l 15% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.8 mmol/l, mean of night time CGMG was 11.2 mmol/l, CGMG was $<$3.3 mmol/l 1.2% of the time (0.9% at night), and $>$10 mmol/l 40% of the time. Symptoms of hypoglycemia were reported 6 times during the BP period and 7 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 4 times during the BP period and 7 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

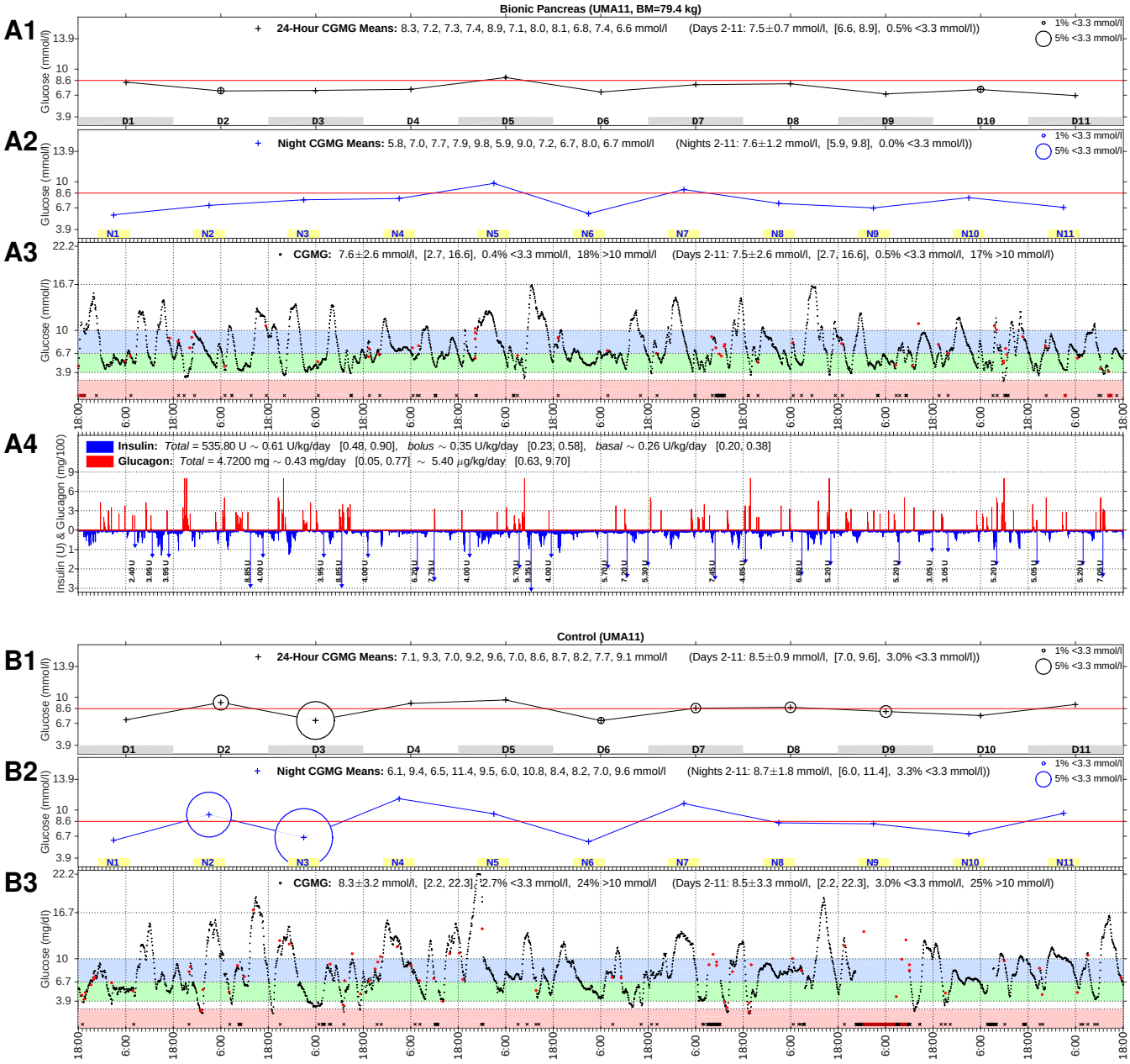


Figure S22. Outpatient experiments in subject #UMA11. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.5 mmol/l, mean of night time CGMG was 7.6 mmol/l, insulin–glucagon dosing was respectively 0.61 U/kg/day and 5.44 μg/kg/day, CGMG was $<$3.3 mmol/l 0.5% of the time (0% at night) and $>$10 mmol/l 17% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.4 mmol/l, mean of night time CGMG was 8.7 mmol/l, CGMG was $<$3.3 mmol/l 3.0% of the time (3.2% at night), and $>$10 mmol/l 25% of the time. Symptoms of hypoglycemia were reported 4 times during the BP period and 4 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported once during the BP period and 4 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

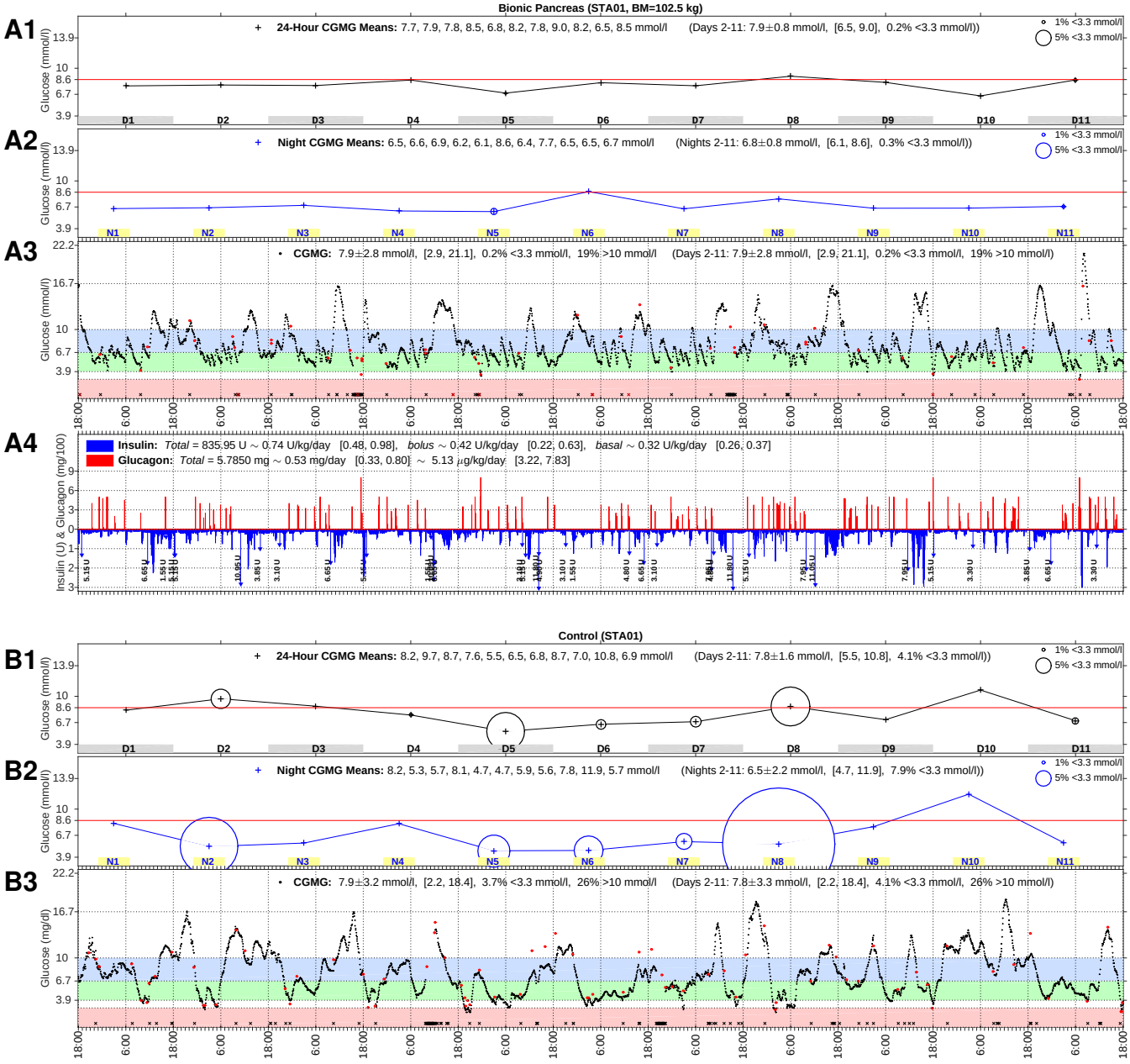


Figure S23. Outpatient experiments in subject #STA01. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.9 mmol/l, mean of night time CGMG was 6.8 mmol/l, insulin–glucagon dosing was respectively 0.74 U/kg/day and 5.26 μg/kg/day, CGMG was $<$3.3 mmol/l 0.2% of the time (0.2% at night) and $>$10 mmol/l 19% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.8 mmol/l, mean of night time CGMG was 6.6 mmol/l, CGMG was $<$3.3 mmol/l 4.1% of the time (7.8% at night), and $>$10 mmol/l 26% of the time. Symptoms of hypoglycemia were reported 4 times during the BP period and 24 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 3 times during the BP period and 24 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/5/6/4/0/7/5/5/9 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported 3 episodes of vomiting on 3 days during the BP period thought to be related to glucagon dosing and no vomiting during the comparator period.

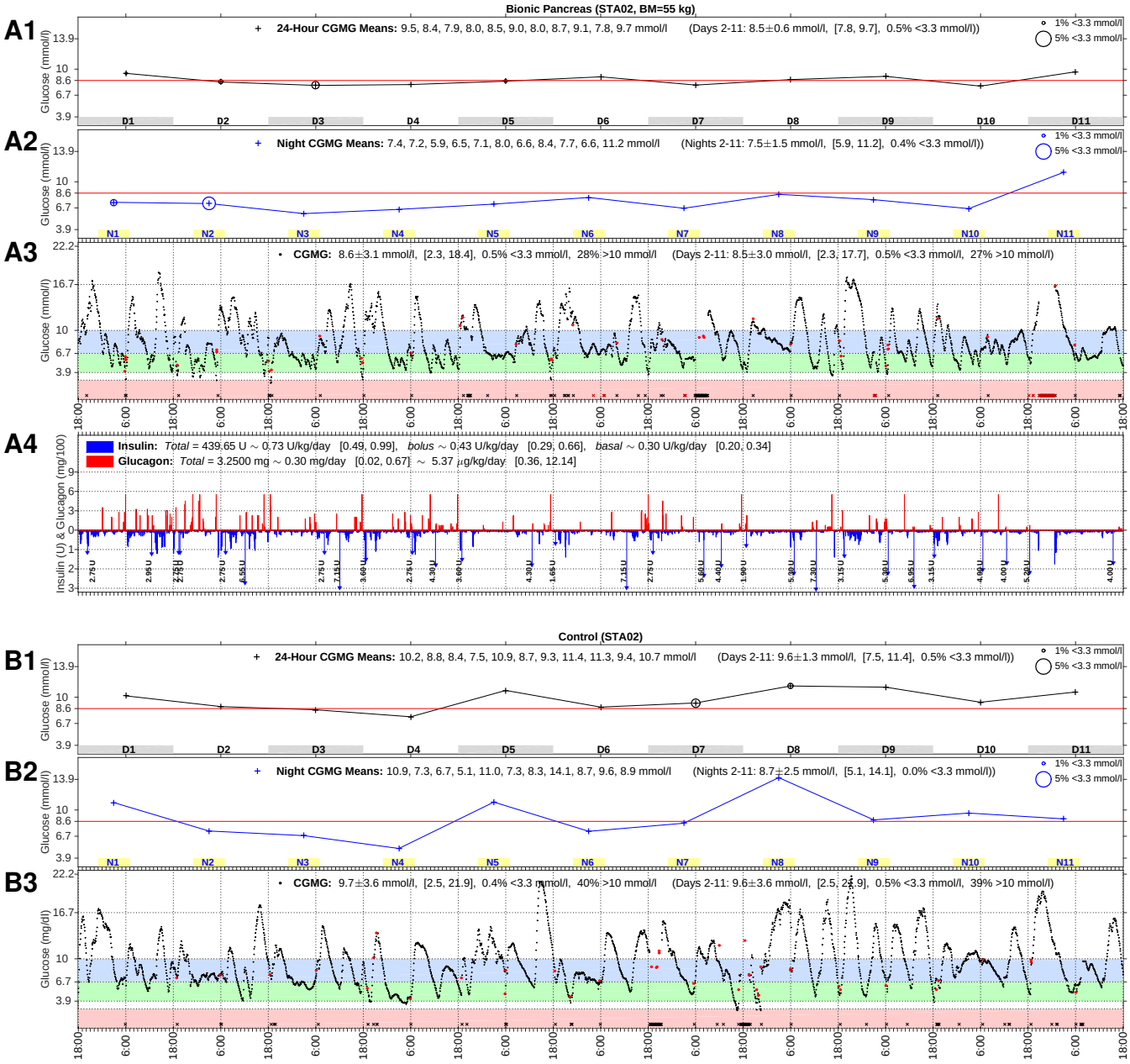


Figure S24. Outpatient experiments in subject #STA02. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.5 mmol/l, mean of night time CGMG was 7.5 mmol/l, insulin–glucagon dosing was respectively 0.71 U/kg/day and 5.02 μg/kg/day, CGMG was $<$3.3 mmol/l 0.5% of the time (0.4% at night) and $>$10 mmol/l 27% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.6 mmol/l, mean of night time CGMG was 8.7 mmol/l, CGMG was $<$3.3 mmol/l 0.5% of the time (0% at night), and $>$10 mmol/l 39% of the time. Symptoms of hypoglycemia were reported 12 times during the BP period and 6 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 10 times during the BP period and 6 times during the comparator period. Daily nausea scores on a scale of 0–10 were 3/0/0/0/0/0/0/4/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

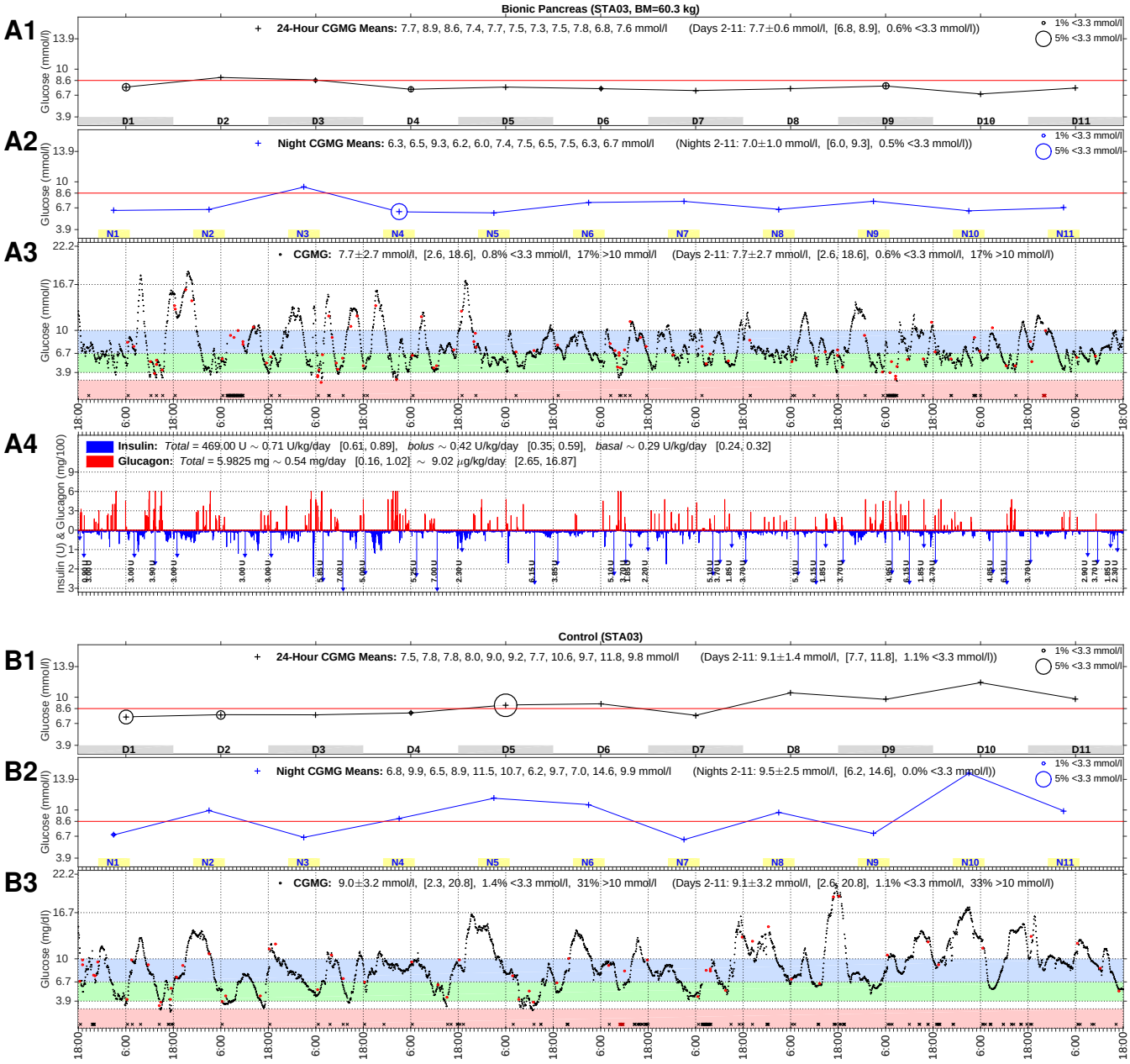


Figure S25. Outpatient experiments in subject #STA03. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.7 mmol/l, mean of night time CGMG was 7.0 mmol/l, insulin–glucagon dosing was respectively 0.71 U/kg/day and 8.23 μg/kg/day, CGMG was $<$3.3 mmol/l 0.6% of the time (0.5% at night) and $>$10 mmol/l 17% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.1 mmol/l, mean of night time CGMG was 9.5 mmol/l, CGMG was $<$3.3 mmol/l 1.1% of the time (0% at night), and $>$10 mmol/l 33% of the time. Symptoms of hypoglycemia were reported 3 times during the BP period and 6 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 5 times during the BP period and 6 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/2/0/0/0 during the comparator period. The subject reported no vomiting in either period.

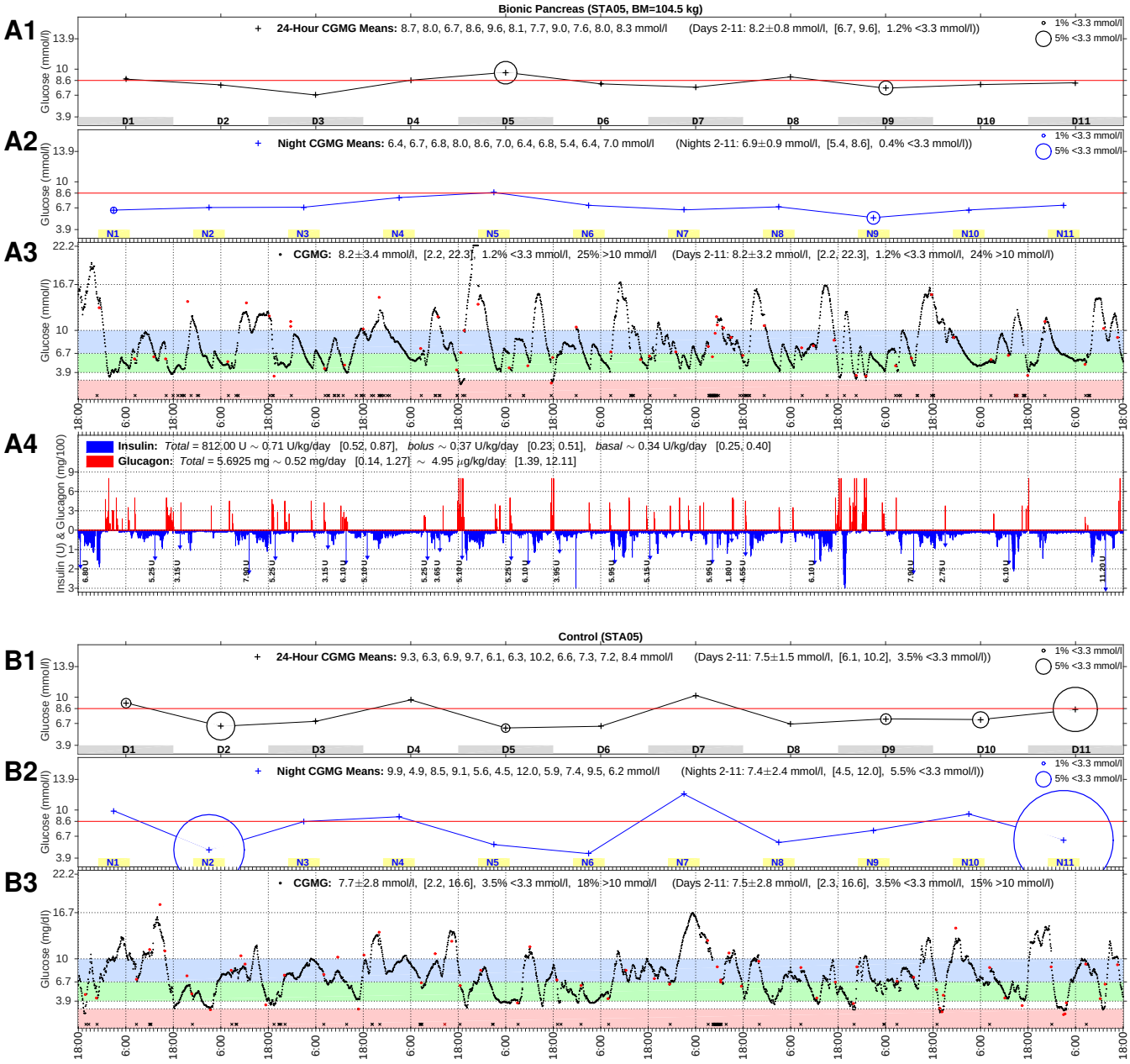


Figure S26. Outpatient experiments in subject #STA05. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.2 mmol/l, mean of night time CGMG was 6.9 mmol/l, insulin–glucagon dosing was respectively 0.70 U/kg/day and 4.56 μg/kg/day, CGMG was $<$3.3 mmol/l 1.2% of the time (0.4% at night) and $>$10 mmol/l 24% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.5 mmol/l, mean of night time CGMG was 7.3 mmol/l, CGMG was $<$3.3 mmol/l 3.5% of the time (5.5% at night), and $>$10 mmol/l 15% of the time. Symptoms of hypoglycemia were reported 5 times during the BP period and 6 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 5 times during the BP period and 7 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

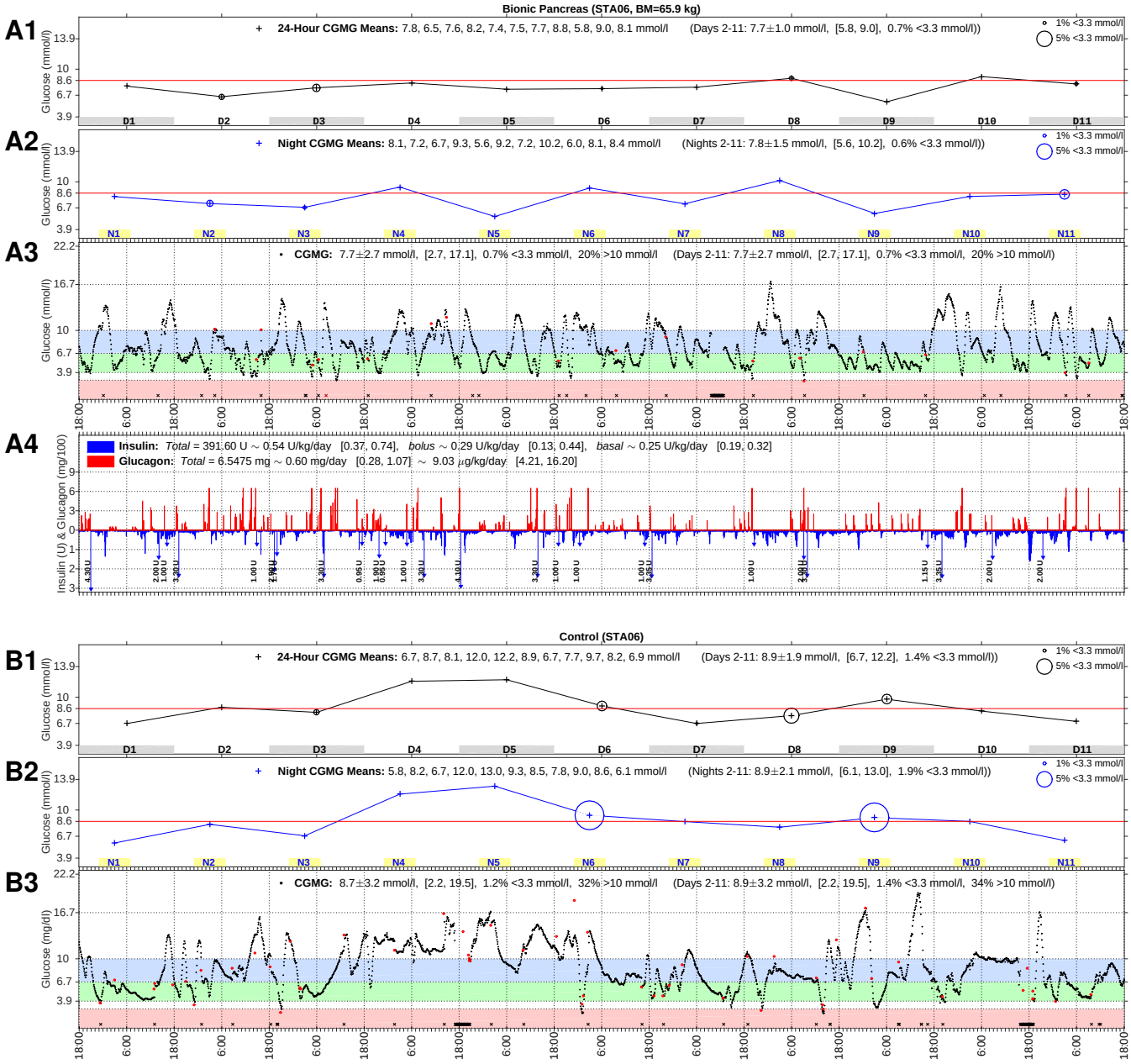


Figure S27. Outpatient experiments in subject #STA06. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.7 mmol/l, mean of night time CGMG was 7.8 mmol/l, insulin–glucagon dosing was respectively 0.54 U/kg/day and 9.28 μg/kg/day, CGMG was $<$3.3 mmol/l 0.7% of the time (0.6% at night) and $>$10 mmol/l 20% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.9 mmol/l, mean of night time CGMG was 8.9 mmol/l, CGMG was $<$3.3 mmol/l 1.4% of the time (1.9% at night), and $>$10 mmol/l 34% of the time. Symptoms of hypoglycemia were reported once during the BP period and 8 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported twice during the BP period and 8 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

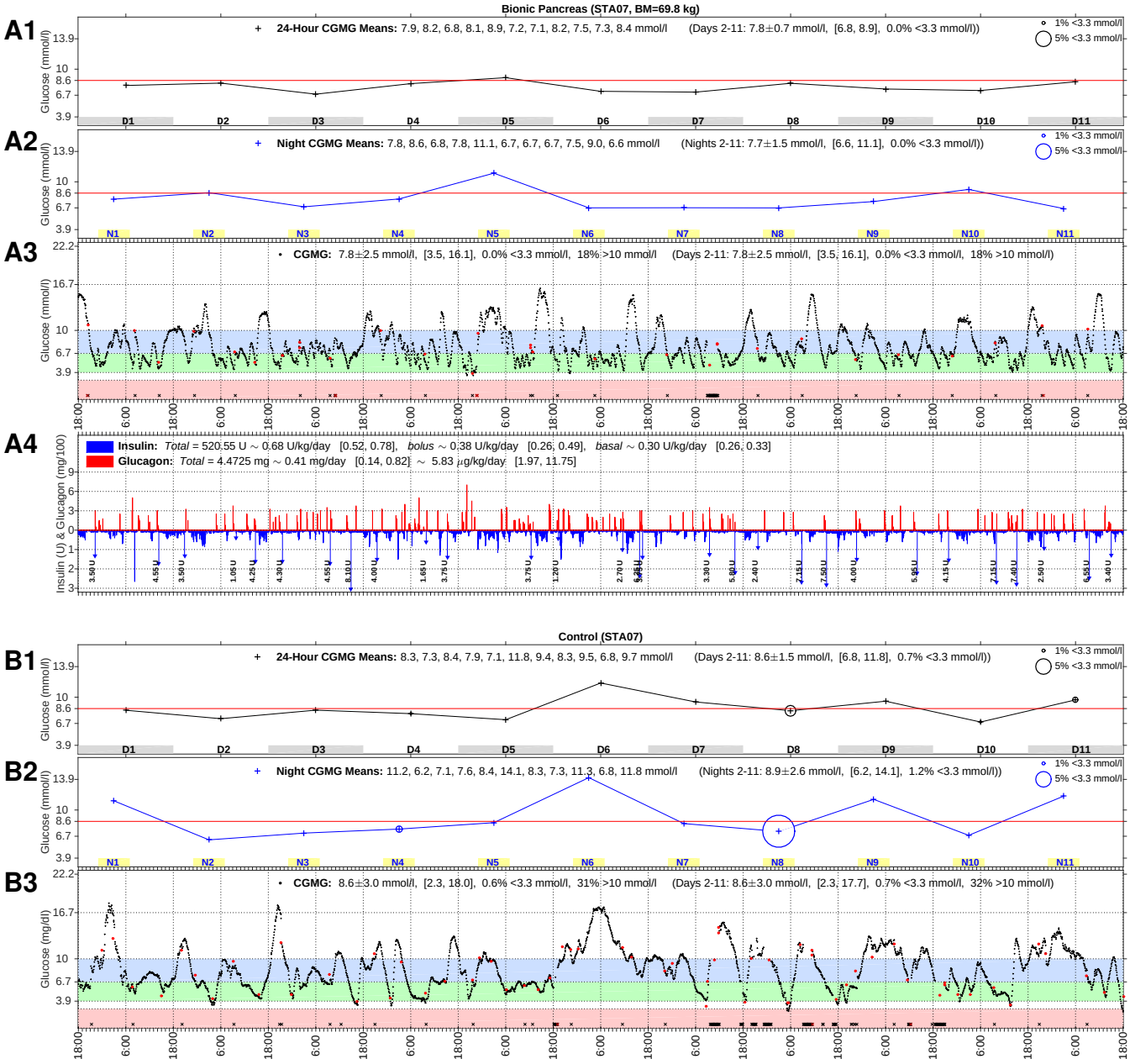


Figure S28. Outpatient experiments in subject #STA07. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.8 mmol/l, mean of night time CGMG was 7.8 mmol/l, insulin–glucagon dosing was respectively 0.68 U/kg/day and 5.91 μg/kg/day, CGMG was $<$3.3 mmol/l 0% of the time (0% at night) and $>$10 mmol/l 18% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 8.6 mmol/l, mean of night time CGMG was 8.9 mmol/l, CGMG was $<$3.3 mmol/l 0.7% of the time (1.2% at night), and $>$10 mmol/l 32% of the time. Symptoms of hypoglycemia were reported 4 times during the BP period and 8 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 4 times during the BP period and 8 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/1/3/0/3/3/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

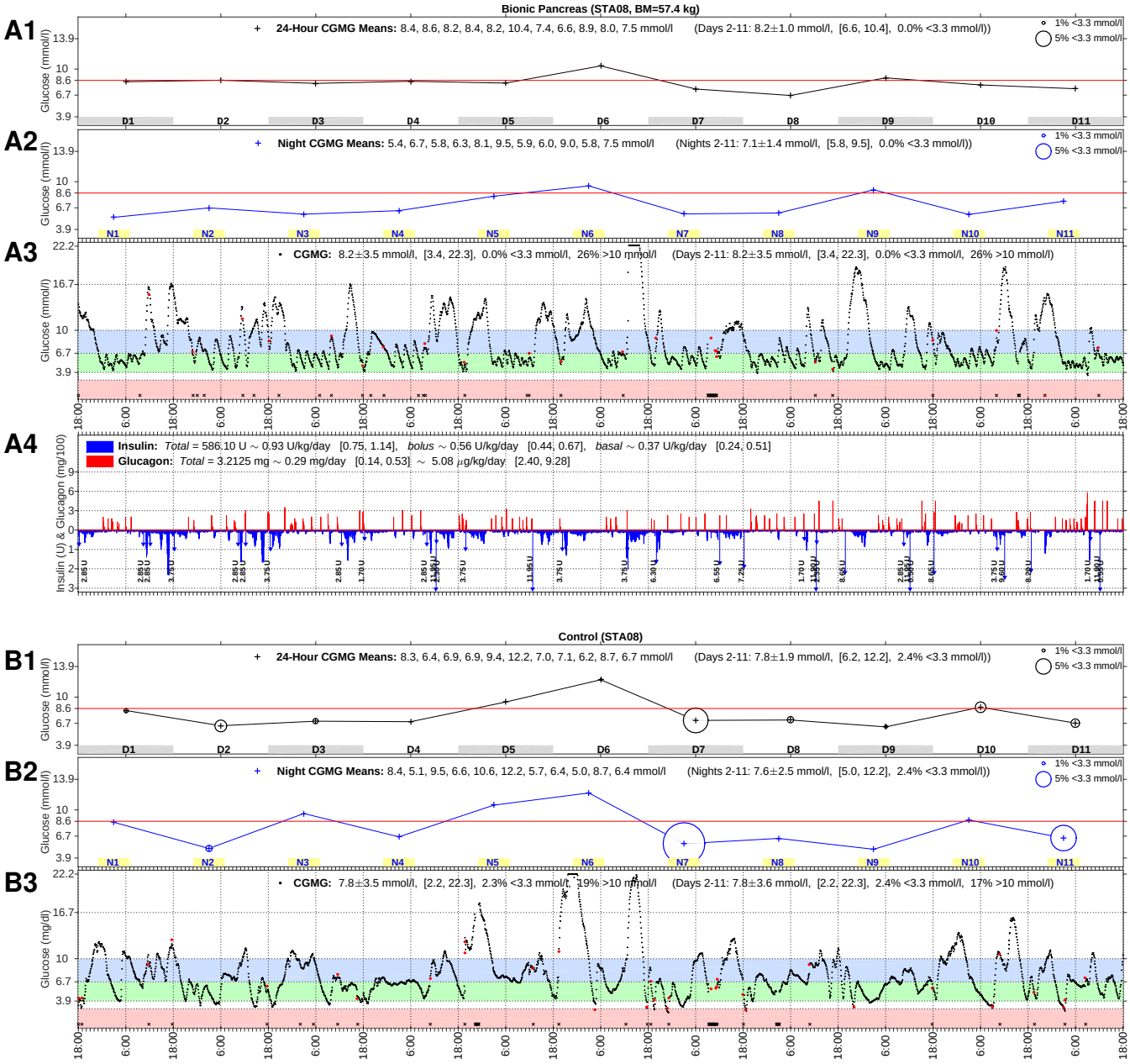


Figure S29. Outpatient experiments in subject #STA08. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.2 mmol/l, mean of night time CGMG was 7.1 mmol/l, insulin–glucagon dosing was respectively 0.92 U/kg/day and 5.29 μg/kg/day, CGMG was $<$3.3 mmol/l 0% of the time (0% at night) and $>$10 mmol/l 26% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.8 mmol/l, mean of night time CGMG was 7.6 mmol/l, CGMG was $<$3.3 mmol/l 2.4% of the time (2.4% at night), and $>$10 mmol/l 17% of the time. Symptoms of hypoglycemia were reported as not occurring during the BP period and 18 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and 18 times during the comparator period. Daily nausea scores on a scale of 0–10 were 2/0/0/0/0/0/0/3/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

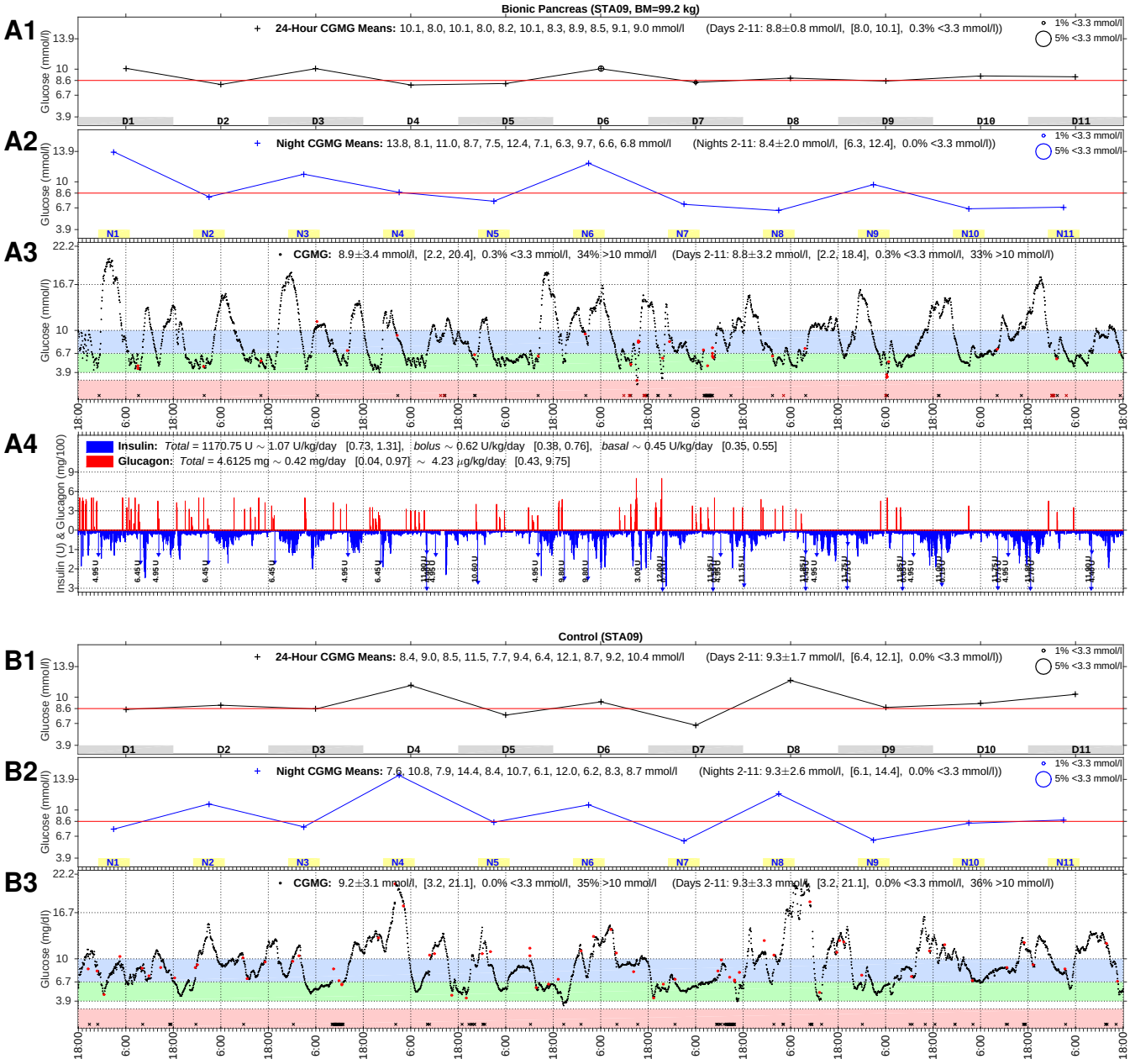


Figure S30. Outpatient experiments in subject #STA09. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.8 mmol/l, mean of night time CGMG was 8.4 mmol/l, insulin–glucagon dosing was respectively 1.07 U/kg/day and 3.67 μg/kg/day, CGMG was $<$3.3 mmol/l 0.3% of the time (0% at night) and $>$10 mmol/l 33% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.3 mmol/l, mean of night time CGMG was 9.3 mmol/l, CGMG was $<$3.3 mmol/l 0% of the time (0% at night), and $>$10 mmol/l 36% of the time. Symptoms of hypoglycemia were reported twice during the BP period and 3 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported twice during the BP period and 3 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

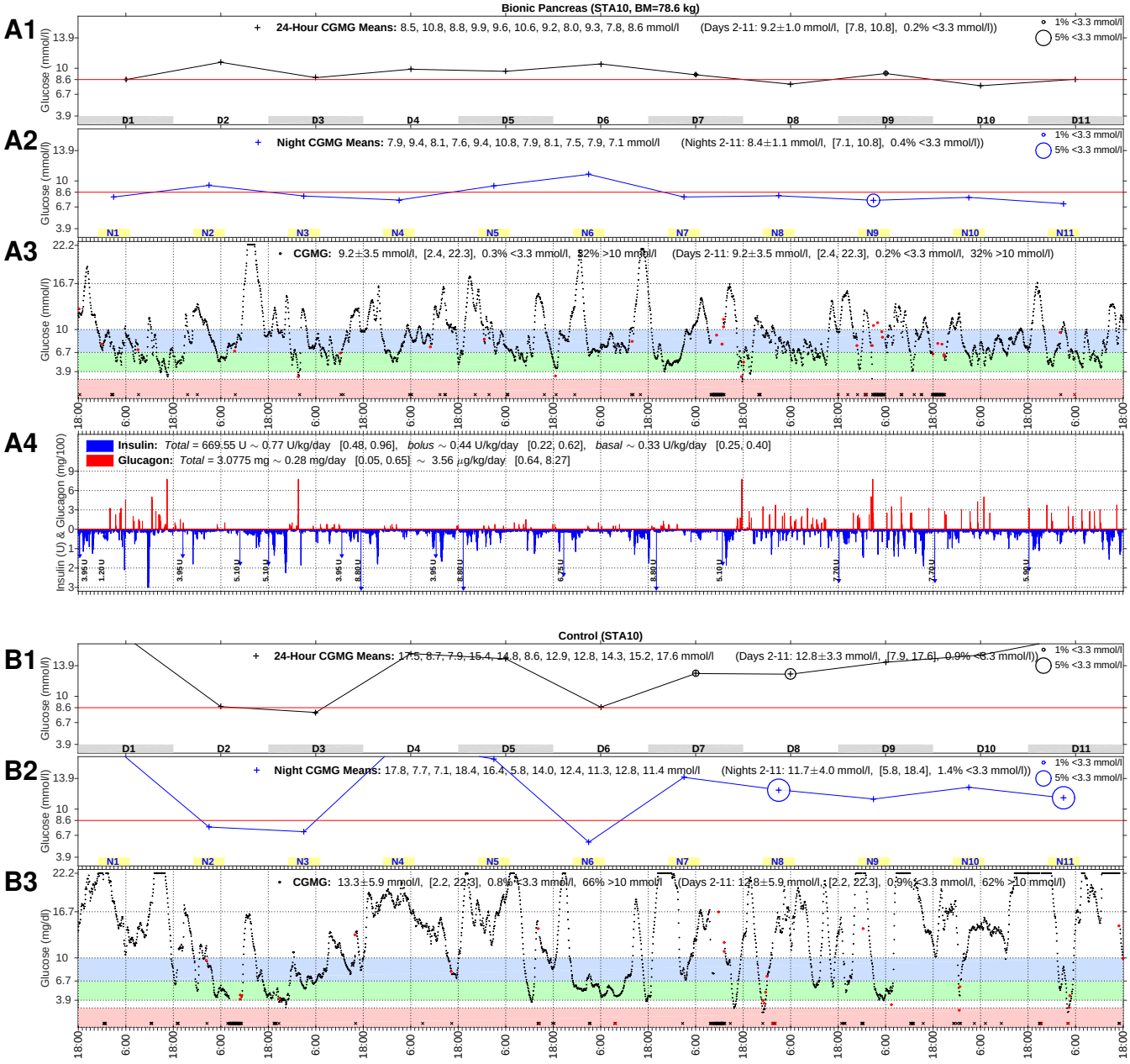


Figure S31. Outpatient experiments in subject #STA10. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 9.2 mmol/l, mean of night time CGMG was 8.4 mmol/l, insulin–glucagon dosing was respectively 0.76 U/kg/day and 3.09 μg/kg/day, CGMG was $<$3.3 mmol/l 0.2% of the time (0.4% at night) and $>$10 mmol/l 32% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 12.8 mmol/l, mean of night time CGMG was 11.7 mmol/l, CGMG was $<$3.3 mmol/l 0.9% of the time (1.5% at night), and $>$10 mmol/l 62% of the time. Symptoms of hypoglycemia were reported 7 times during the BP period and 13 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 5 times during the BP period and 13 times during the comparator period. Daily nausea scores on a scale of 0–10 were 6/4/0/0/2/3/7/3/0/0/0 during the BP period, and 0/0/0/2/0/0/0/0/0/0/0 during the comparator period. The subject reported 2 episodes of vomiting on two days during the BP period and no vomiting during the comparator period.

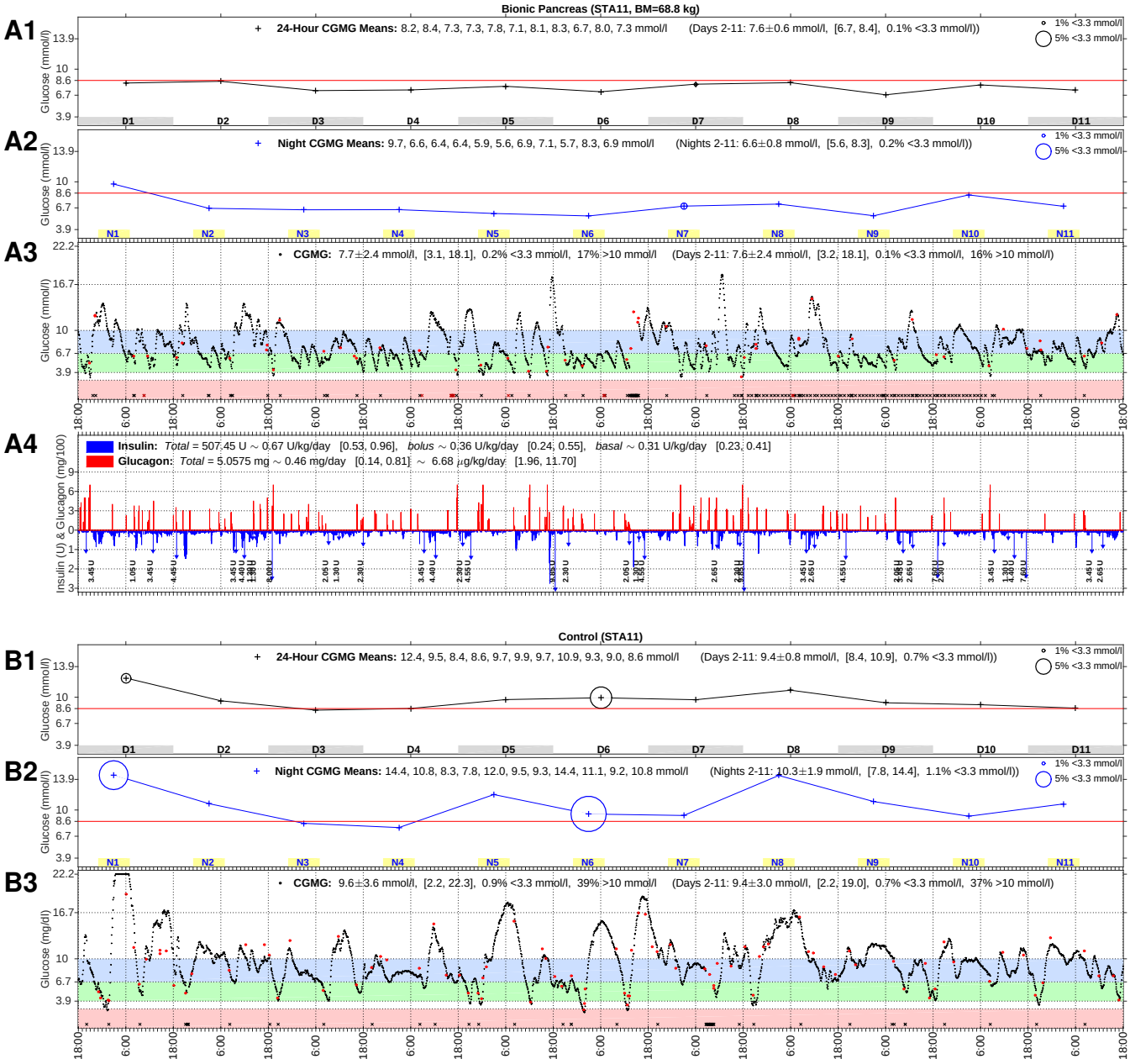


Figure S32. Outpatient experiments in subject #STA11. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.6 mmol/l, mean of night time CGMG was 6.6 mmol/l, insulin–glucagon dosing was respectively 0.66 U/kg/day and 6.33 μg/kg/day, CGMG was $<$3.3 mmol/l 0.1% of the time (0.2% at night) and $>$10 mmol/l 16% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.3 mmol/l, mean of night time CGMG was 10.3 mmol/l, CGMG was $<$3.3 mmol/l 0.7% of the time (1.1% at night), and $>$10 mmol/l 37% of the time. Symptoms of hypoglycemia were reported 8 times during the BP period and 4 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 8 times during the BP period and 4 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/4/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

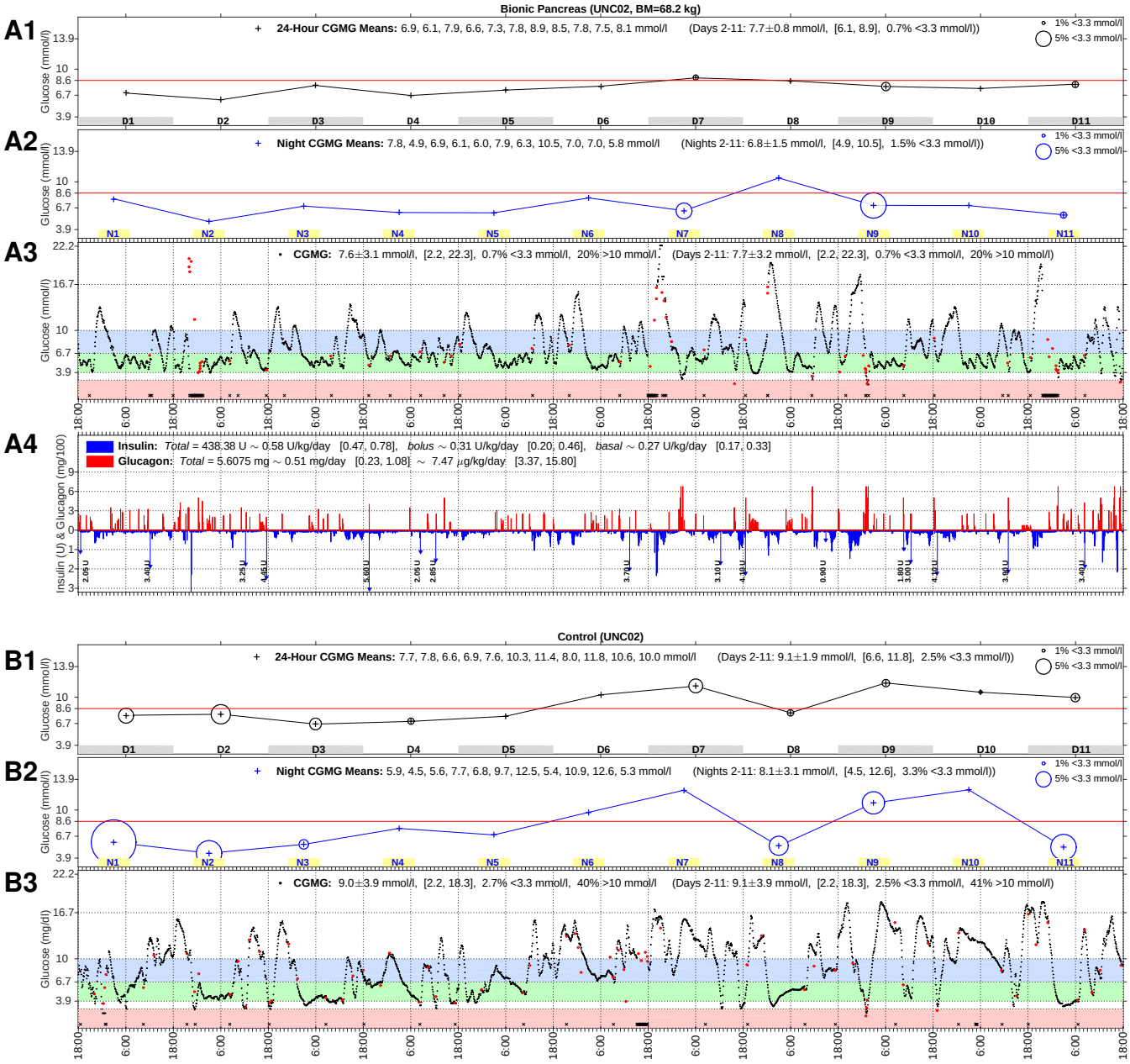


Figure S33. Outpatient experiments in subject #UNC02. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.7 mmol/l, mean of night time CGMG was 6.8 mmol/l, insulin–glucagon dosing was respectively 0.59 U/kg/day and 7.43 μg/kg/day, CGMG was $<$3.3 mmol/l 0.7% of the time (1.6% at night) and $>$10 mmol/l 20% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.1 mmol/l, mean of night time CGMG was 8.1 mmol/l, CGMG was $<$3.3 mmol/l 2.5% of the time (3.3% at night), and $>$10 mmol/l 41% of the time. Symptoms of hypoglycemia were reported 10 times during the BP period and 11 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 8 times during the BP period and 11 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/1/1/4/1/1/1/1 during the BP period, and 0/3/1/1/0/0/1/1/1/1/1 during the comparator period. The subject reported no vomiting in either period.

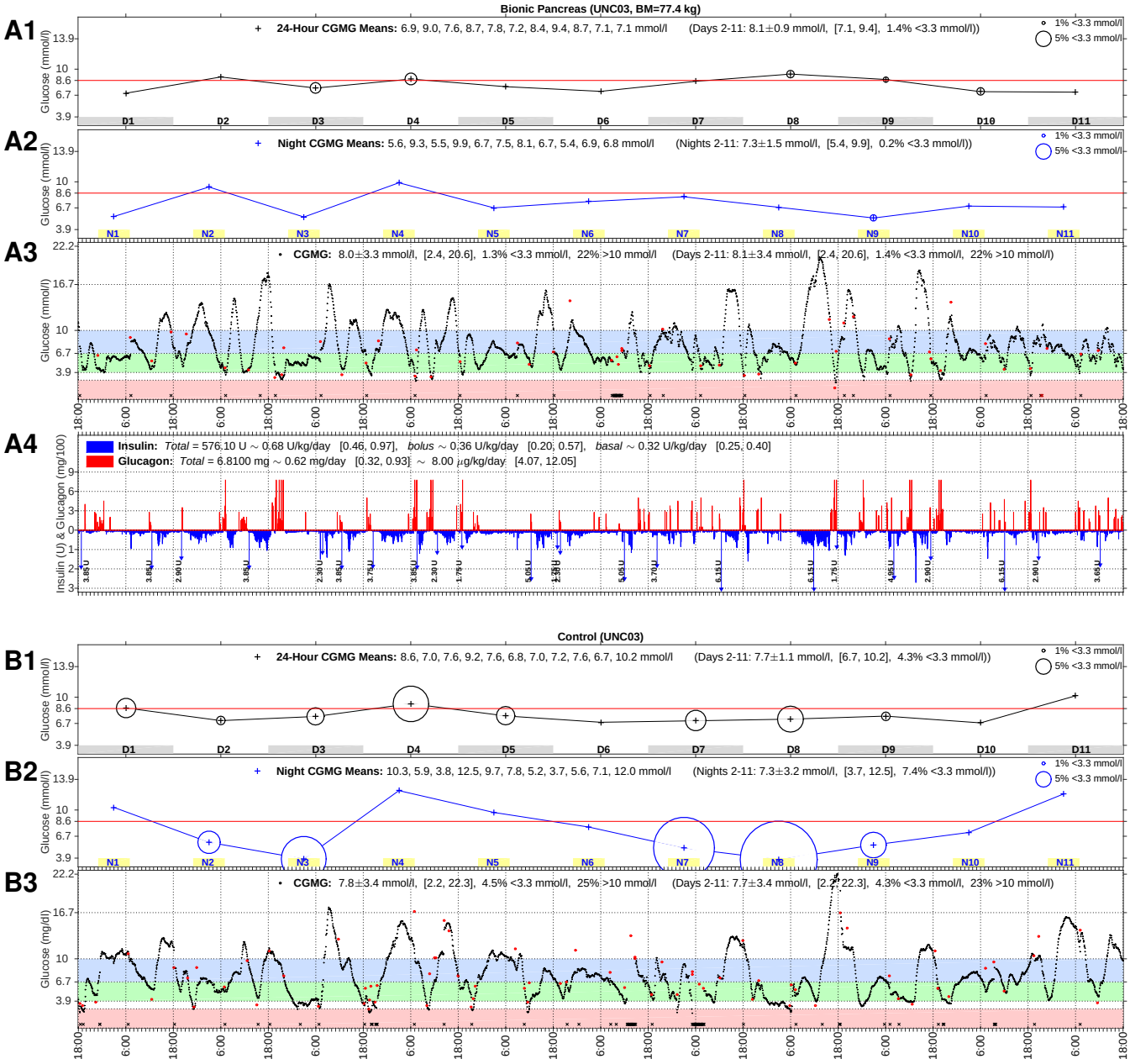


Figure S34. Outpatient experiments in subject #UNC03. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.1 mmol/l, mean of night time CGMG was 7.3 mmol/l, insulin–glucagon dosing was respectively 0.70 U/kg/day and 8.34 μg/kg/day, CGMG was $<$3.3 mmol/l 1.4% of the time (0.2% at night) and $>$10 mmol/l 22% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.7 mmol/l, mean of night time CGMG was 7.3 mmol/l, CGMG was $<$3.3 mmol/l 4.3% of the time (7.4% at night), and $>$10 mmol/l 23% of the time. Symptoms of hypoglycemia were reported 3 times during the BP period and 13 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 4 times during the BP period and 14 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/5/0/0 during the BP period, and 0/0/0/2/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

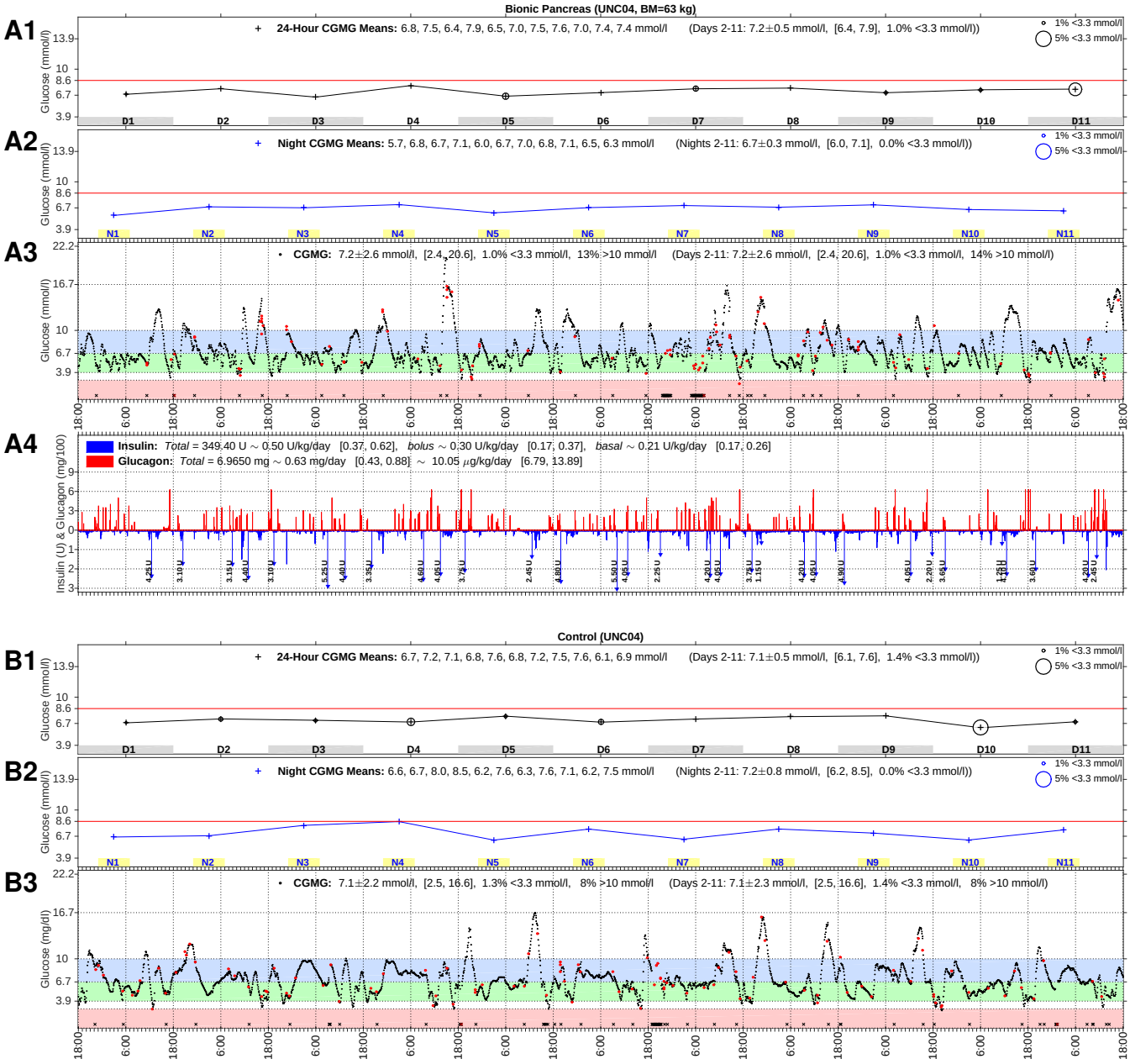


Figure S35. Outpatient experiments in subject #UNC04. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.2 mmol/l, mean of night time CGMG was 6.7 mmol/l, insulin–glucagon dosing was respectively 0.52 U/kg/day and 10.16 μg/kg/day, CGMG was $<$3.3 mmol/l 1.0% of the time (0% at night) and $>$10 mmol/l 14% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.1 mmol/l, mean of night time CGMG was 7.2 mmol/l, CGMG was $<$3.3 mmol/l 1.4% of the time (0% at night), and $>$10 mmol/l 8% of the time. Symptoms of hypoglycemia were reported 19 times during the BP period and 17 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 14 times during the BP period and 28 times during the comparator period. Daily nausea scores on a scale of 0–10 were 5/2/0/3/0/0/0/2/2/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

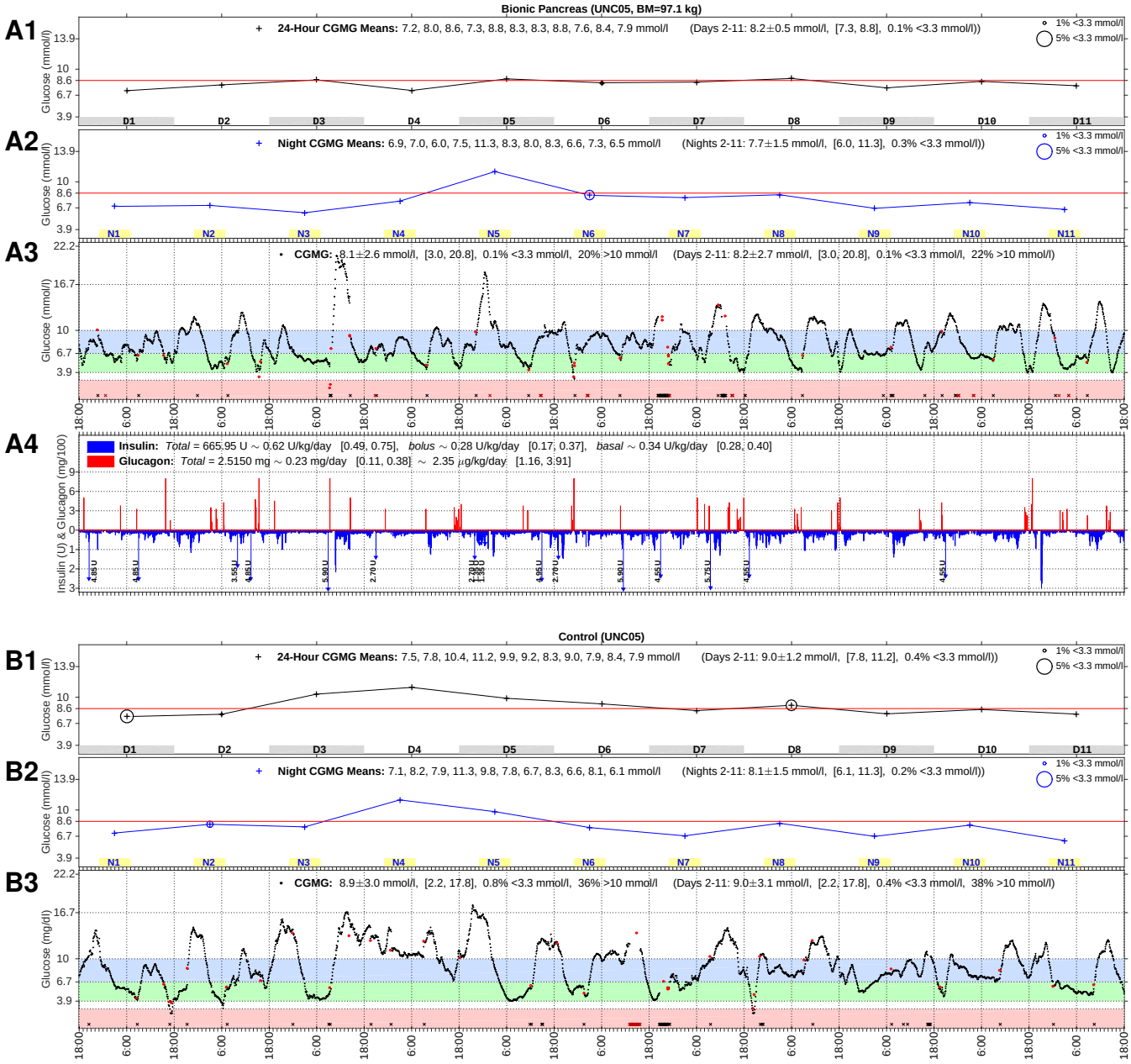


Figure S36. Outpatient experiments in subject #UNC05. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.2 mmol/l, mean of night time CGMG was 7.7 mmol/l, insulin–glucagon dosing was respectively 0.64 U/kg/day and 2.37 μg/kg/day, CGMG was $<$3.3 mmol/l 0.1% of the time (0.3% at night) and $>$10 mmol/l 22% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.0 mmol/l, mean of night time CGMG was 8.1 mmol/l, CGMG was $<$3.3 mmol/l 0.4% of the time (0.2% at night), and $>$10 mmol/l 38% of the time. Symptoms of hypoglycemia were reported 8 times during the BP period and 6 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 5 times during the BP period and 4 times during the comparator period. Daily nausea scores on a scale of 0–10 were 3/0/6/0/0/4/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

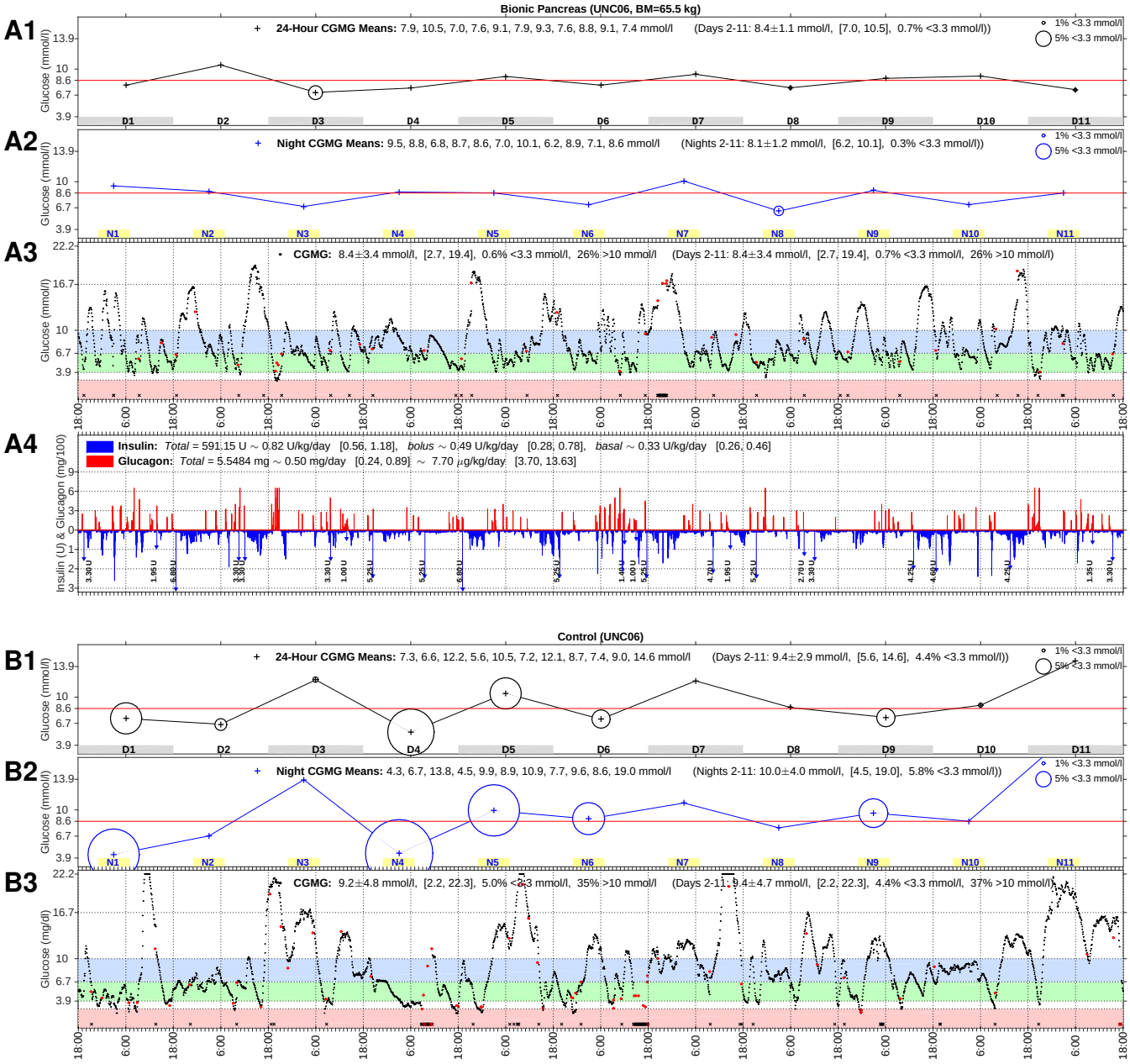


Figure S37. Outpatient experiments in subject #UNC06. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.4 mmol/l, mean of night time CGMG was 8.1 mmol/l, insulin–glucagon dosing was respectively 0.83 U/kg/day and 7.18 μg/kg/day, CGMG was $<$3.3 mmol/l 0.7% of the time (0.3% at night) and $>$10 mmol/l 26% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 9.4 mmol/l, mean of night time CGMG was 10 mmol/l, CGMG was $<$3.3 mmol/l 4.4% of the time (5.8% at night), and $>$10 mmol/l 37% of the time. Symptoms of hypoglycemia were reported twice during the BP period and 15 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and 13 times during the comparator period. Daily nausea scores on a scale of 0–10 were 2/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

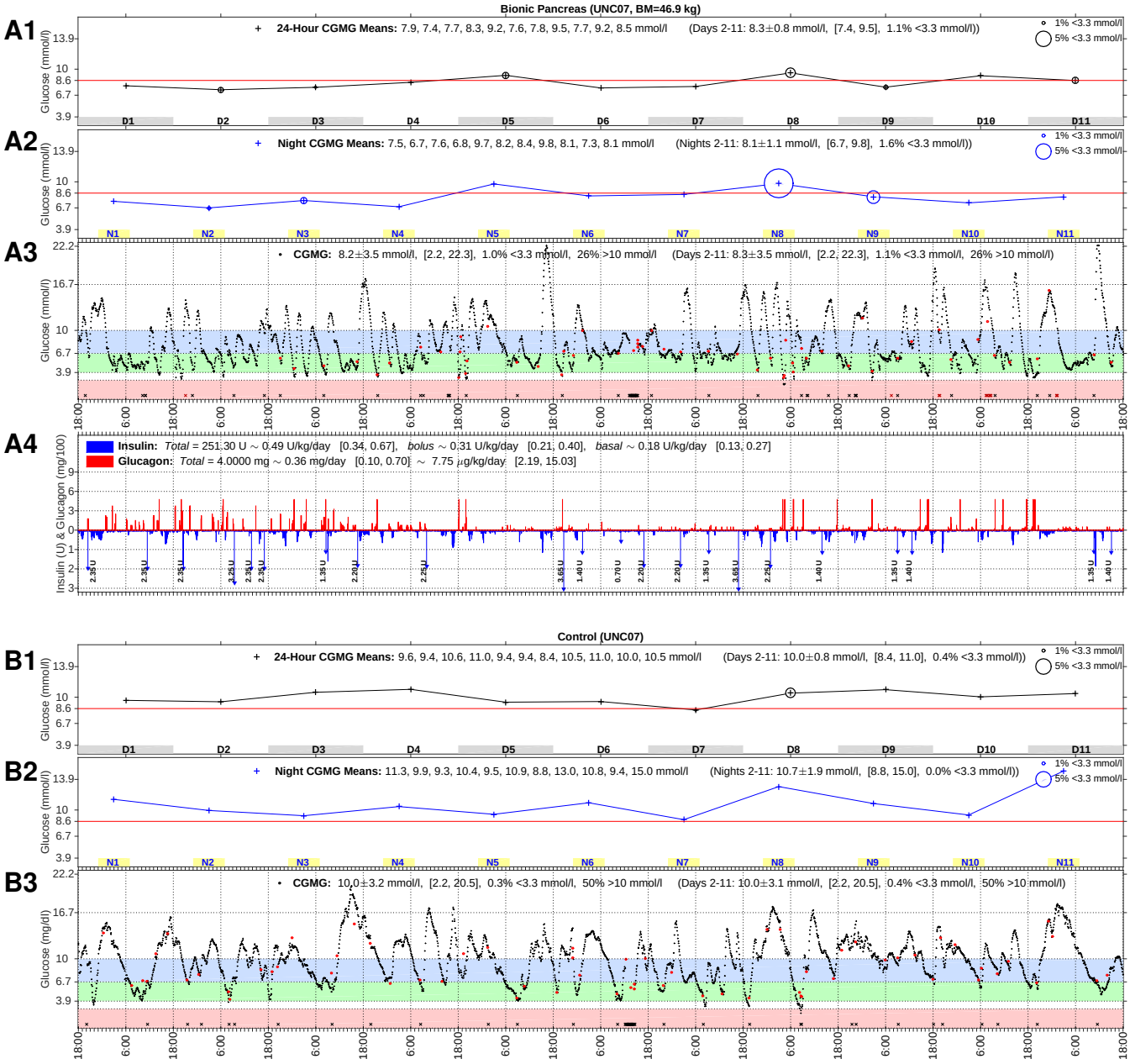


Figure S38. Outpatient experiments in subject #UNC07. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.3 mmol/l, mean of night time CGMG was 8.1 mmol/l, insulin–glucagon dosing was respectively 0.47 U/kg/day and 7.43 μg/kg/day, CGMG was $<$3.3 mmol/l 1.1% of the time (1.7% at night) and $>$10 mmol/l 26% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 10 mmol/l, mean of night time CGMG was 10.7 mmol/l, CGMG was $<$3.3 mmol/l 0.4% of the time (0% at night), and $>$10 mmol/l 50% of the time. Symptoms of hypoglycemia were reported 8 times during the BP period and twice during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 8 times during the BP period and twice during the comparator period. Daily nausea scores on a scale of 0–10 were 0/4/3/0/0/0/0/3/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

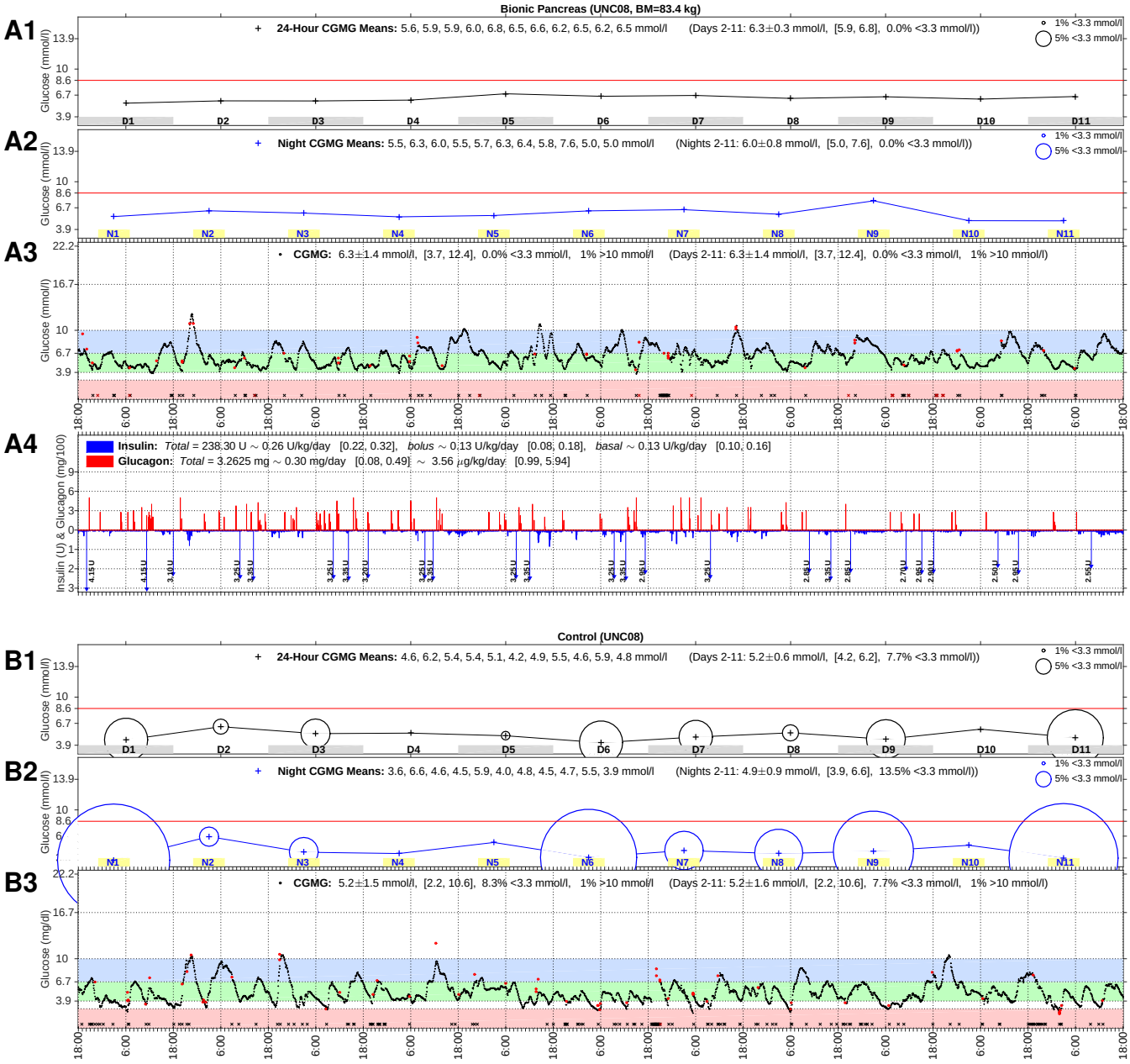


Figure S39. Outpatient experiments in subject #UNC08. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 6.3 mmol/l, mean of night time CGMG was 5.9 mmol/l, insulin–glucagon dosing was respectively 0.26 U/kg/day and 3.40 μg/kg/day, CGMG was $<$3.3 mmol/l 0% of the time (0% at night) and $>$10 mmol/l 1% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 5.2 mmol/l, mean of night time CGMG was 4.9 mmol/l, CGMG was $<$3.3 mmol/l 7.7% of the time (13.3% at night), and $>$10 mmol/l 1% of the time. Symptoms of hypoglycemia were reported as not occurring during the BP period and 5 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and 19 times during the comparator period. Daily nausea scores on a scale of 0–10 were 0/0/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

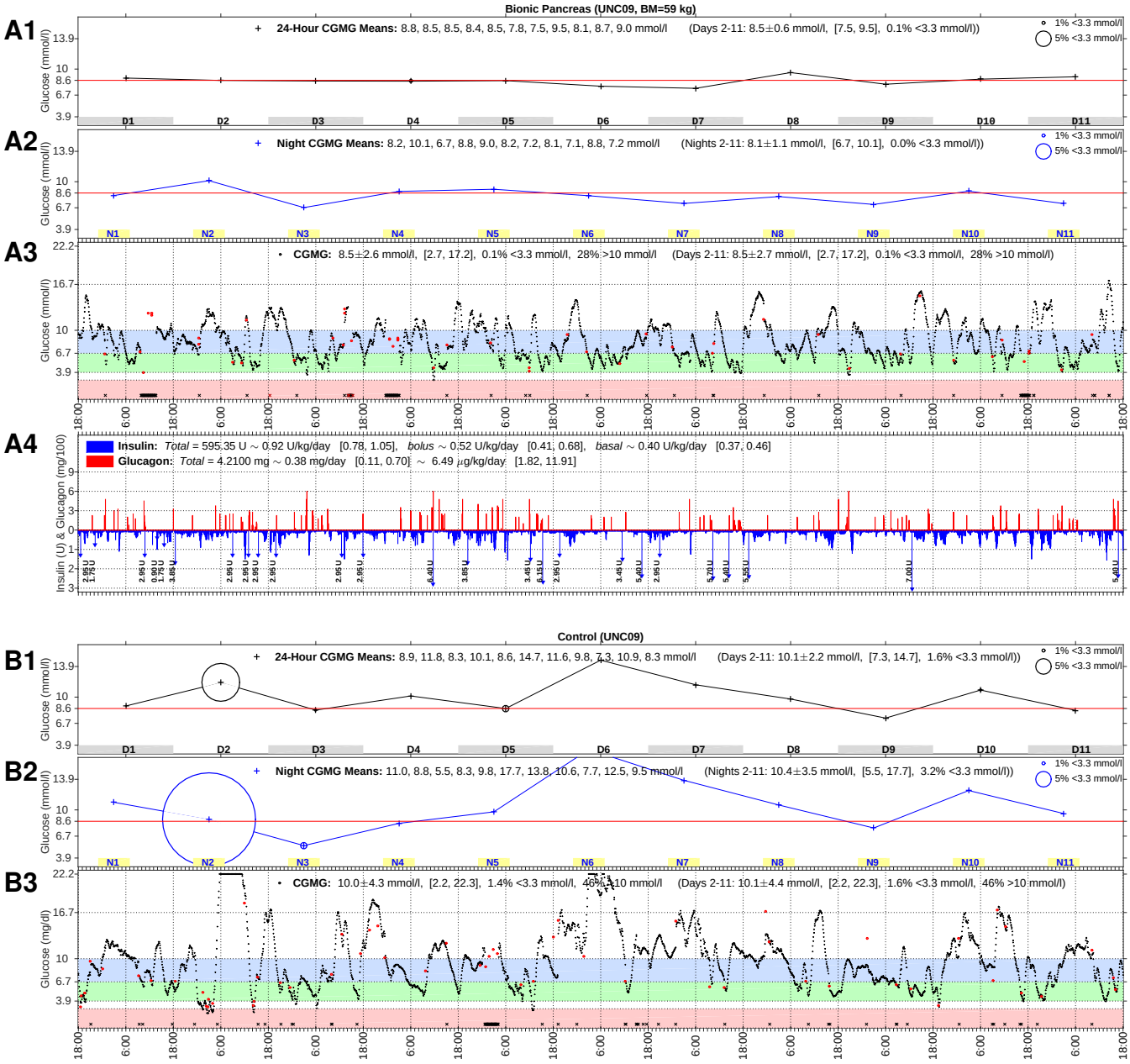


Figure S40. Outpatient experiments in subject #UNC09. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 8.4 mmol/l, mean of night time CGMG was 8.1 mmol/l, insulin–glucagon dosing was respectively 0.93 U/kg/day and 6.54 μg/kg/day, CGMG was $<$3.3 mmol/l 0.1% of the time (0% at night) and $>$10 mmol/l 28% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 10.2 mmol/l, mean of night time CGMG was 10.4 mmol/l, CGMG was $<$3.3 mmol/l 1.6% of the time (3.2% at night), and $>$10 mmol/l 46% of the time. Symptoms of hypoglycemia were reported twice during the BP period and 22 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported as not occurring during the BP period and 22 times during the comparator period. Daily nausea scores on a scale of 0–10 were 3/0/0/0/0/0/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

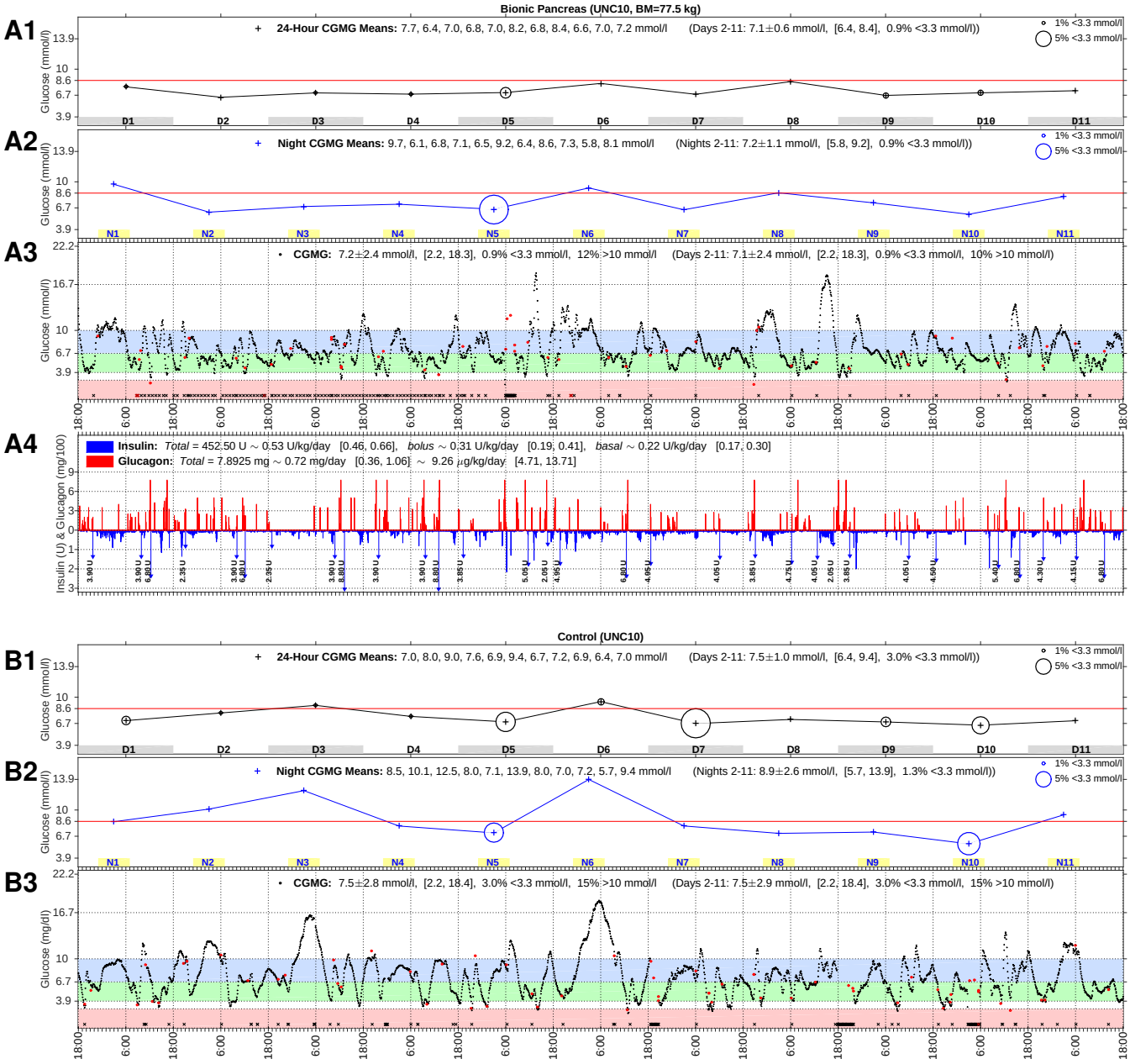


Figure S41. Outpatient experiments in subject #UNC10. See Figure S3 for explanation of layout of panels. Beyond the first 24 hours, after the BP has undergone most of its online adaptation, mean CGMG was 7.1 mmol/l, mean of night time CGMG was 7.2 mmol/l, insulin–glucagon dosing was respectively 0.53 U/kg/day and 8.84 μg/kg/day, CGMG was $<$3.3 mmol/l 0.9% of the time (0.9% at night) and $>$10 mmol/l 10% of the time. On the other hand, beyond the first 24 hours in the comparator period, mean of overall daily CGMG was 7.5 mmol/l, mean of night time CGMG was 8.9 mmol/l, CGMG was $<$3.3 mmol/l 3.0% of the time (1.4% at night), and $>$10 mmol/l 16% of the time. Symptoms of hypoglycemia were reported 8 times during the BP period and 31 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 8 times during the BP period and 33 times during the comparator period. Daily nausea scores on a scale of 0–10 were 3/0/0/4/0/4/4/0/0/0/0 during the BP period, and 0/0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period.

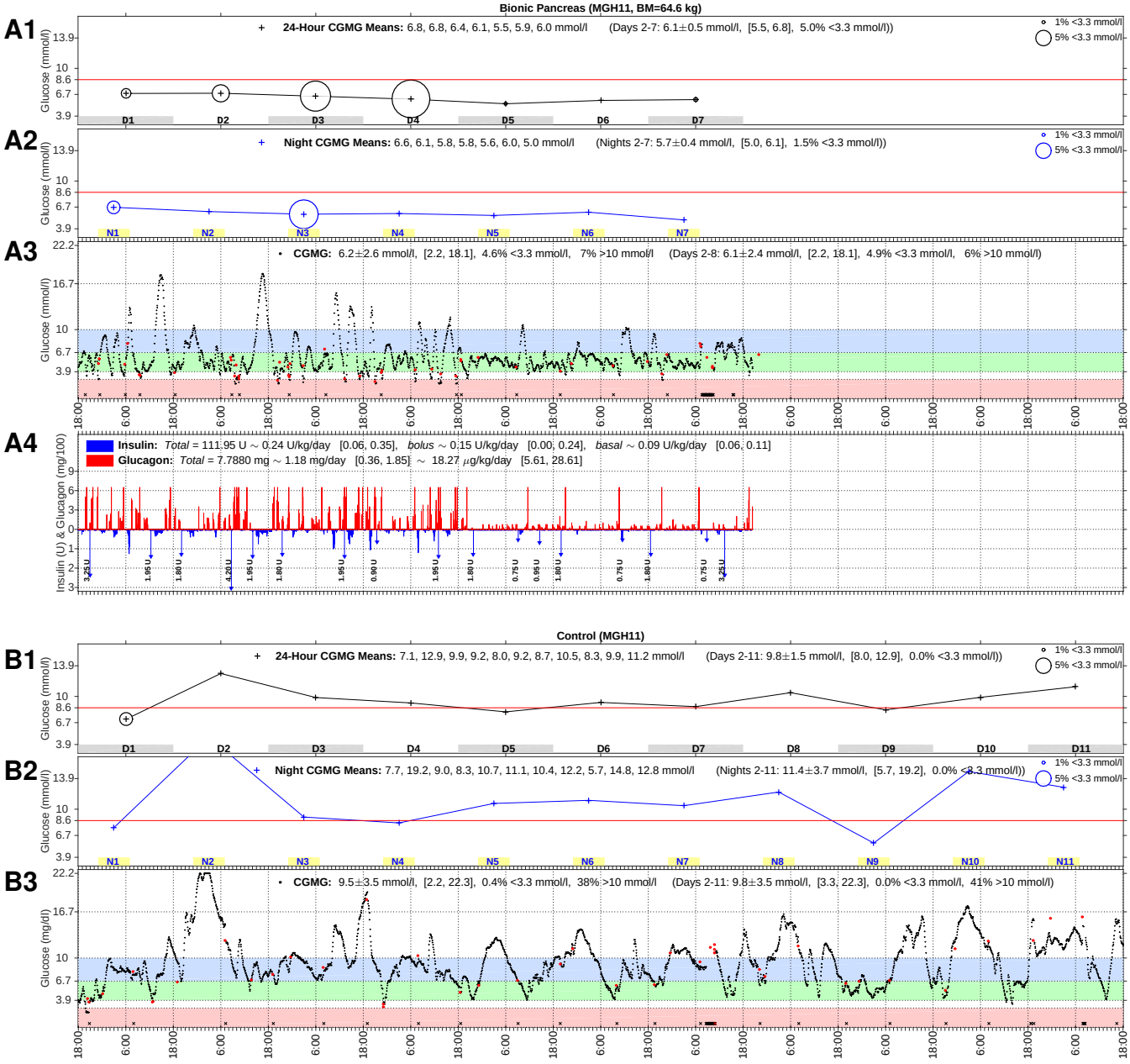


Figure S42. Excluded incomplete outpatient experiments in subject #MGH11. See Figure S3 for explanation of layout of panels. Symptoms of hypoglycemia were reported 6 times during the BP period and 1 time during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 7 times during the BP period and 1 time during the comparator period. Daily nausea scores on a scale of 0–10 were 8/0/3/5/4/5/3 during the BP period, and 0/0/0/0/0/0/0/0/0/0 during the comparator period. The subject reported no vomiting in either period. This subject experienced excessive nausea and hypoglycemia during the first four days of the study, at which point we raised the set point of the BP to 7.2 mmol/l from 5.6 mmol/l. All participants had the option to change their set point from a minimum of 5.6 mmol/l (the default) to a maximum of 7.2 mmol/l. From the time the set point was changed, the subject experienced very good BP control for the next three days. Nonetheless, the subject decided to withdraw from the study shortly after 18:00 on day 7, citing anxiety, inconvenience and continued nausea, and the data is not included in the main analyses.

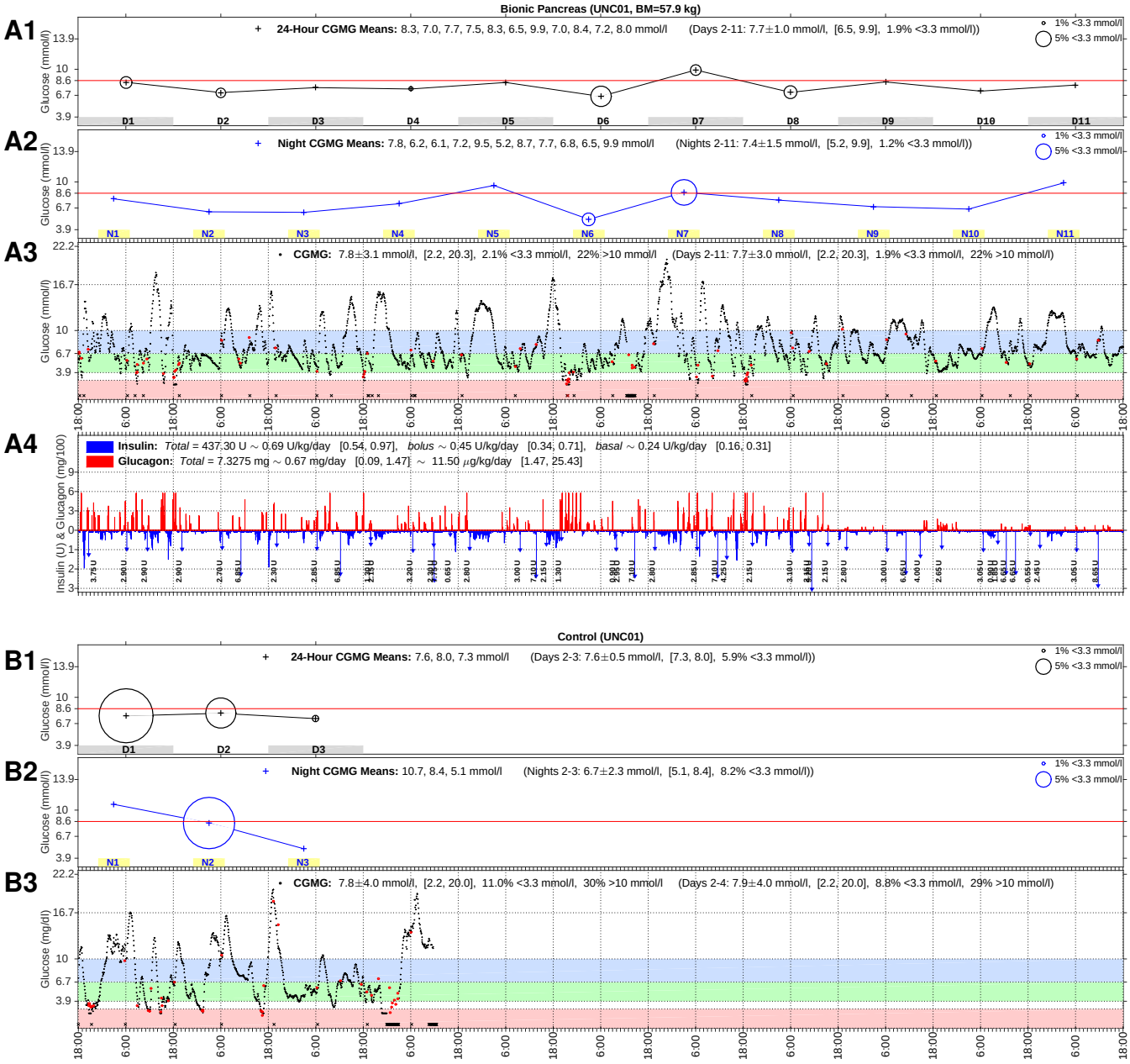


Figure S43. Excluded incomplete outpatient experiments in subject #UNC01. See Figure S3 for explanation of layout of panels. Symptoms of hypoglycemia were reported 3 times during the BP period and 7 times during the comparator period. Hypoglycemia requiring treatment with oral carbohydrates was reported 3 times during the BP period and 7 times during the comparator period. Daily nausea scores on a scale of 0–10 were 3/0/0/0/0/3/0/0/0/0/0 during the BP period, and 0/0/0/8 during the comparator period. The subject reported no vomiting in the BP period and 1 episode of vomiting during the comparator period after treatment of a severe low blood sugar with a full dose of glucagon, and believed it to be related to the glucagon administration. The subject was withdrawn from the study after this severe hypoglycemic event per protocol, and the data is not included in the main analyses.

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