# Supplement: A unified computational model for the human response to lipopolysaccharide-induced inflammation

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This supplementary document shows model simulations for the calibrated unified model with data from Clodi et al. (2008) and Janum et al. (2016) (Figure 1) as well as the four model prediction scenarios described in the main text: the effect of LPS administration time (Figures 2 and 3), the effect of repeated LPS exposure (Figures 4 and 5), the effect of dosage amount in a single LPS injection (Figures 6 and 7), and the effect of a continuous infusion of LPS (Figure 8). All model simulations shown have either extended (six to seven 24-hour cycles) or shortened (one half to two 24-hour cycles) time courses compared the simulations (three to four 24-hour cycles) shown in the main text. These different time courses show a more in-depth view of the unified model's dynamics in response to LPS administration and that, after several cycles, the model returns to steady state. Model parameters and initial conditions used to generate the simulations below are given in Table 1 in the main text.

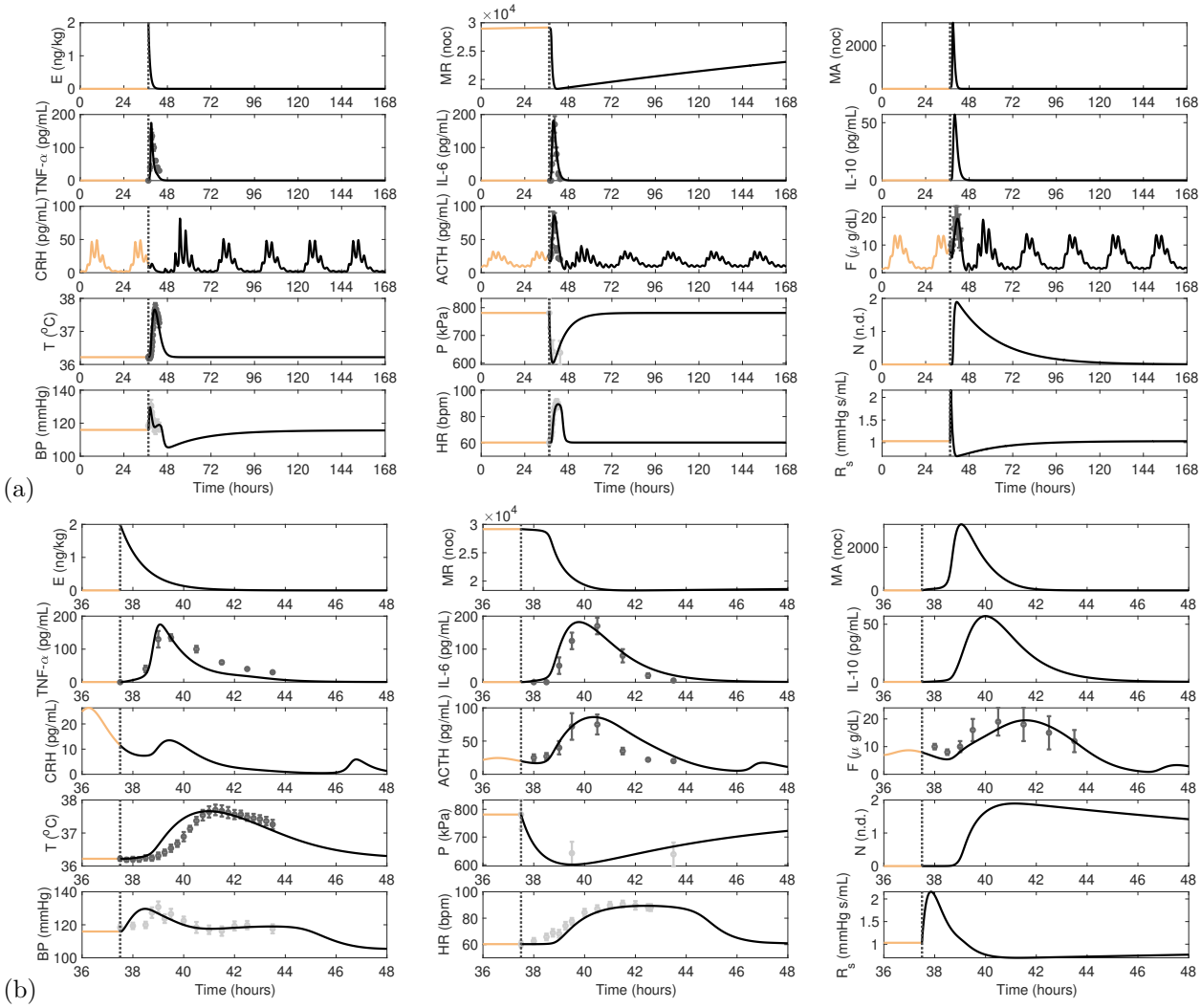


Figure 1: Extended and shortened time course simulation generated by solving the unified model with parameters calibrated to data. LPS is administered at time $t = 37.5$ hours (marked by vertical dotted lines). Results at times before LPS injection are marked by solid orange lines, while solid black lines are used for results at times after LPS injection. Data from Clodi et al. (2008) are shown in dark gray and data from Janum et al. (2016) in light gray (mean ± SE). (a) Simulation run for seven 24-hour cycles. (b) Simulation run for half of one 24-hour cycle.

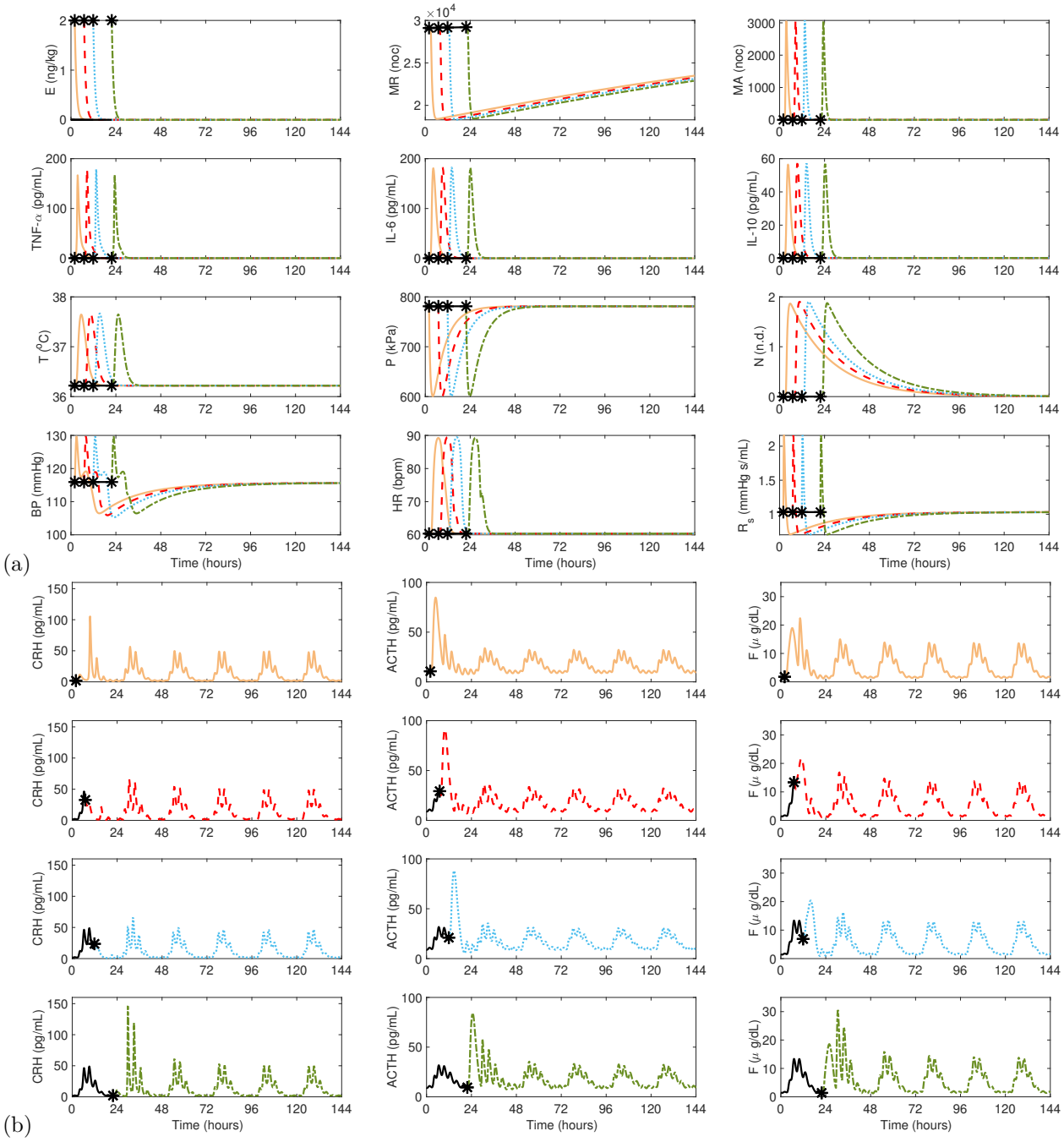


Figure 2: Extended time course model simulations examining the timing of LPS administration. The solid black line denotes the model simulation before LPS administration. Black asterisks mark when LPS is administered (at $t = 2, 7, 11.9$, and 21.8 hours). Post-LPS dynamics are depicted by orange solid lines ($t = 2$), red dashed lines ($t = 7$), blue dotted lines ($t = 11.9$), and green dashed-dotted lines ($t = 21.8$). (a) Inflammatory and cardiovascular simulations. (b) HPA axis simulations.

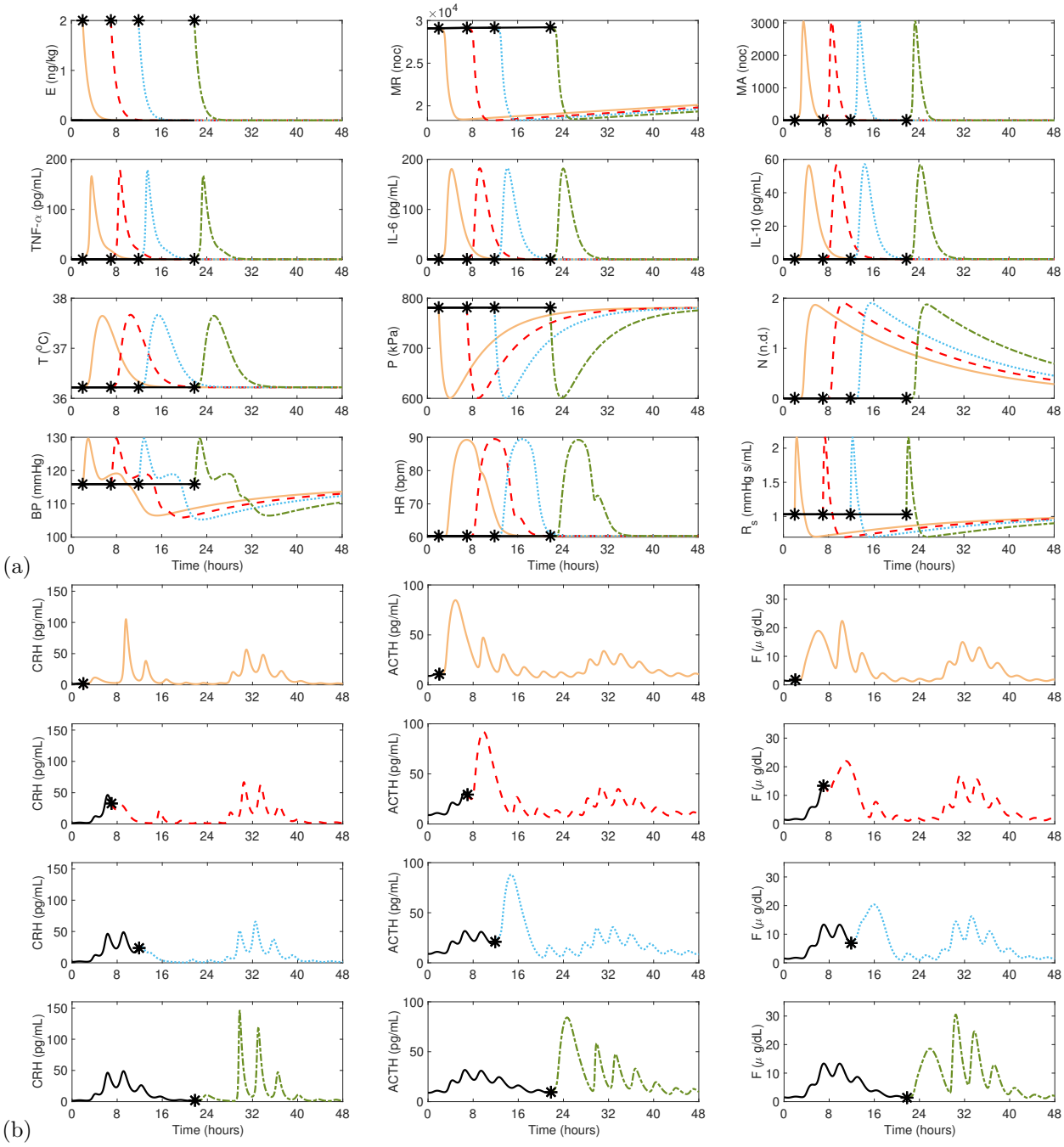


Figure 3: Shortened time course model simulations examining the timing of LPS administration. The solid black line denotes the model simulation before LPS administration. Black asterisks mark when LPS is administered (at $t = 2, 7, 11.9$, and 21.8 hours). Post-LPS dynamics are depicted by orange solid lines ($t = 2$), red dashed lines ($t = 7$), blue dotted lines ($t = 11.9$), and green dashed-dotted lines ($t = 21.8$). (a) Inflammatory and cardiovascular simulations. (b) HPA axis simulations.

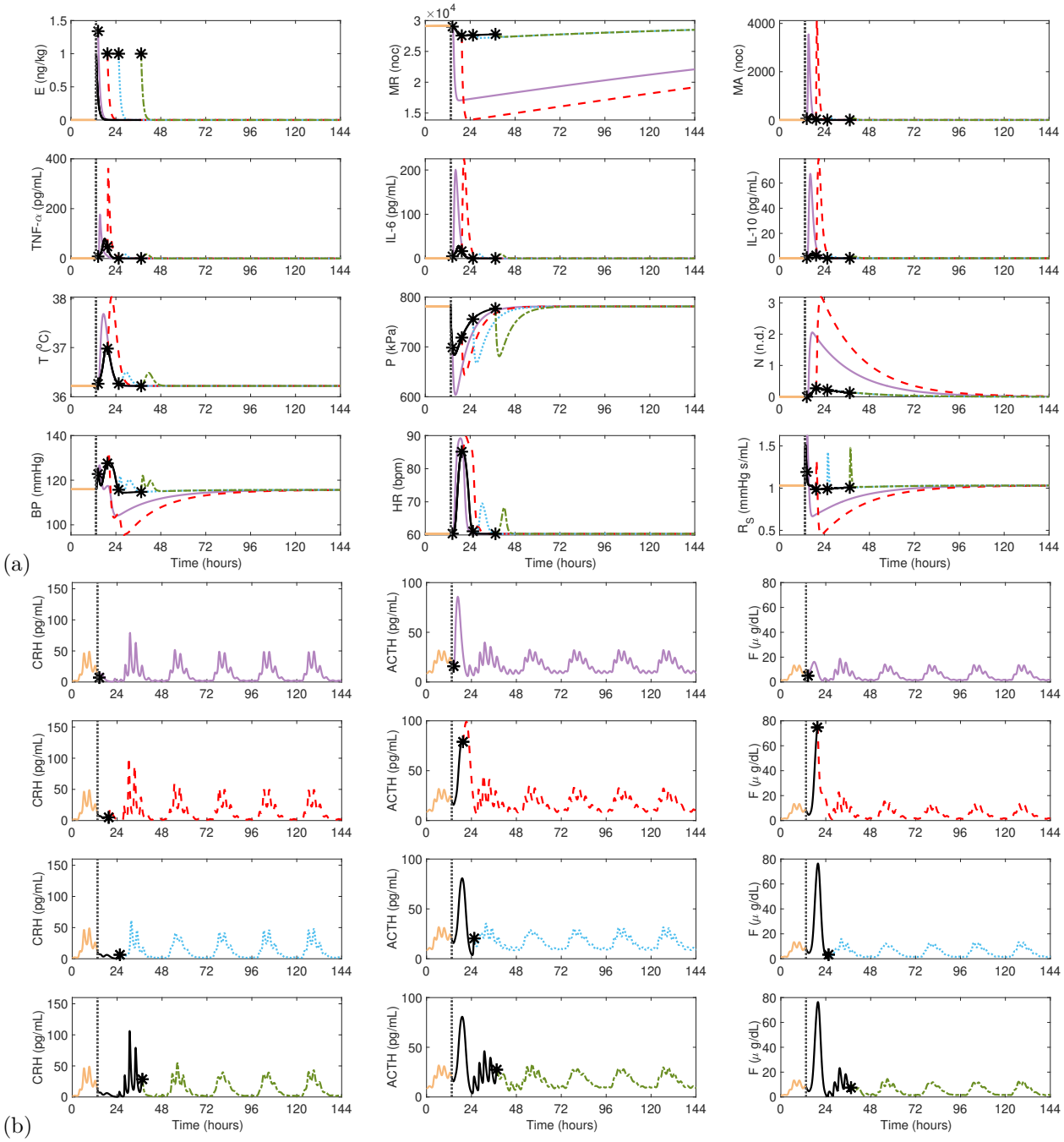


Figure 4: Repeated LPS dose: Extended time course model simulations when 1 ng/kg is administered at $t_1 = 13.5$ hours and 1 ng/kg is administered at $t_2$. The solid orange line denotes the model simulation before the first LPS dose. The vertical dotted line denotes when the first LPS dose is given ($t_1 = 13.5$). The solid black line denotes the model dynamics between the first and second LPS doses. Black asterisks denote when the second LPS dose is given. The second LPS dose is administered at times $t_2 = 14.5, 19.5, 25.5,$ and 37.5 hours. Model dynamics after the second dose of LPS is administered are given by purple solid lines ($t_2 = 14.5$), red dashed lines ($t_2 = 19.5$), blue dotted lines ($t_2 = 25.5$), and green dashed-dotted lines ($t_2 = 37.5$). (a) Inflammatory and cardiovascular simulations. (b) HPA axis simulations.

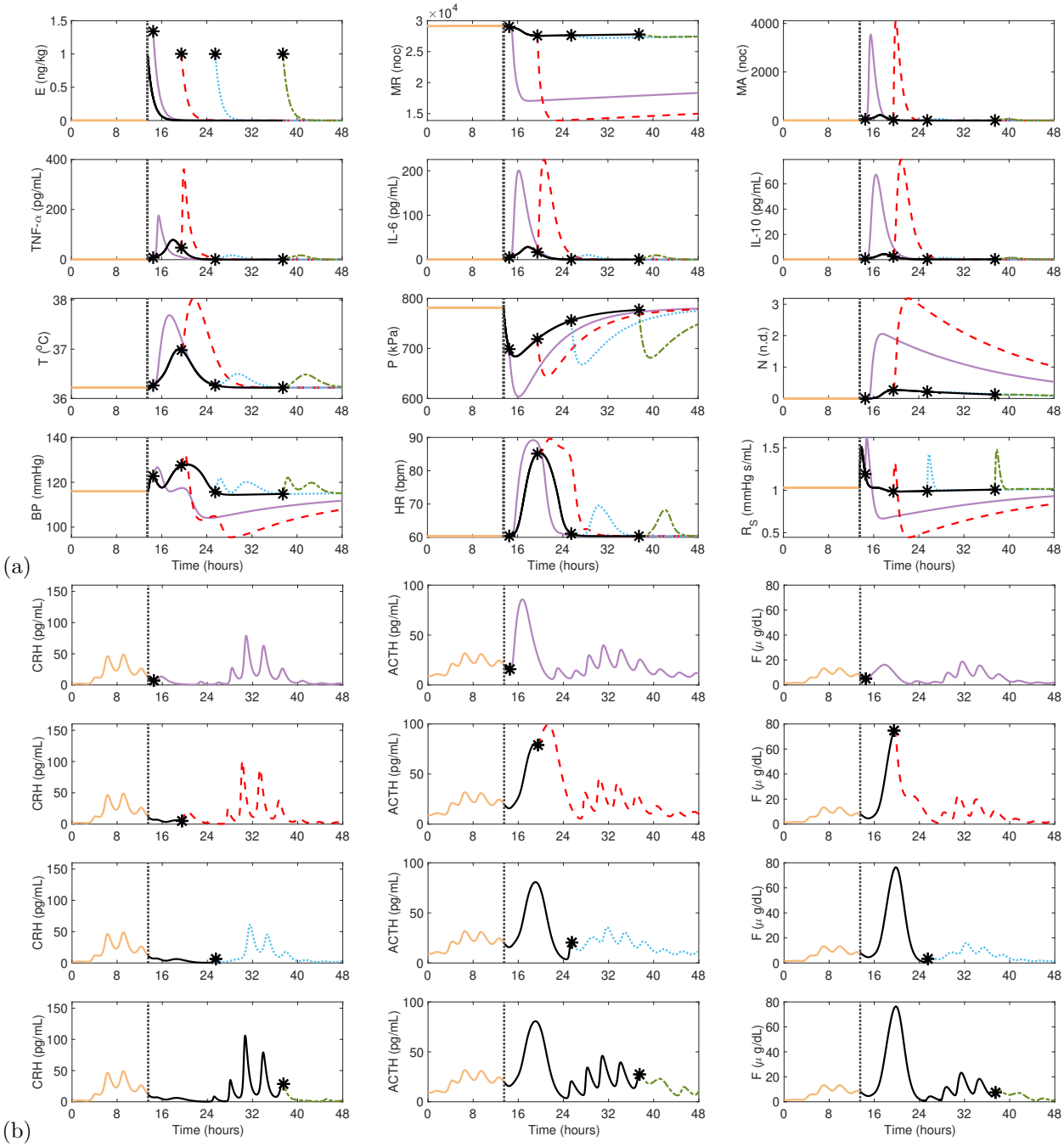


Figure 5: Repeated LPS dose: Shortened time course model simulations when 1 ng/kg is administered at $t_1 = 13.5$ hours and 1 ng/kg is administered at $t_2$. The solid orange line denotes the model simulation before the first LPS dose. The vertical dotted line denotes when the first LPS dose is given ($t_1 = 13.5$). The solid black line denotes the model dynamics between the first and second LPS doses. Black asterisks denote when the second LPS dose is given. The second LPS dose is administered at times $t_2 = 14.5, 19.5, 25.5,$ and 37.5 hours. Model dynamics after the second dose of LPS is administered are given by purple solid lines ($t_2 = 14.5$), red dashed lines ($t_2 = 19.5$), blue dotted lines ($t_2 = 25.5$), and green dashed-dotted lines ($t_2 = 37.5$). (a) Inflammatory and cardiovascular simulations. (b) HPA axis simulations.

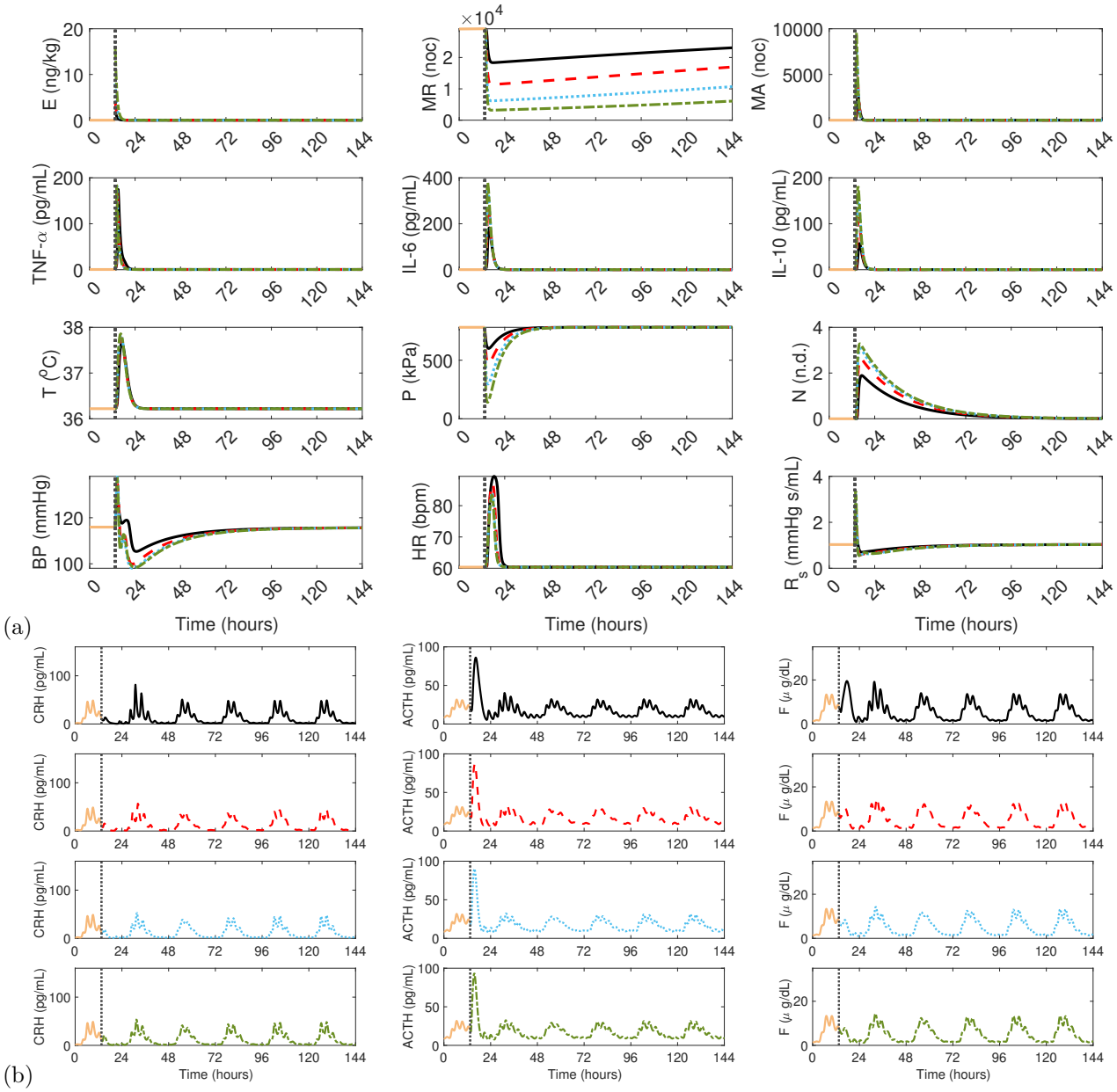


Figure 6: Extended time course model simulations when the total amount of LPS administered as a bolus dose varies. The solid orange line denotes the model simulation before LPS administration. The vertical dotted line indicates when the LPS was given ($t = 13.5$ hours). Post-LPS model dynamics are shown by solid black lines (2 ng/kg), red dashed lines (4 ng/kg), blue dotted lines (8 ng/kg), and green dashed-dotted lines (16 ng/kg). (a) Inflammatory and cardiovascular simulations. (b) HPA axis simulations.

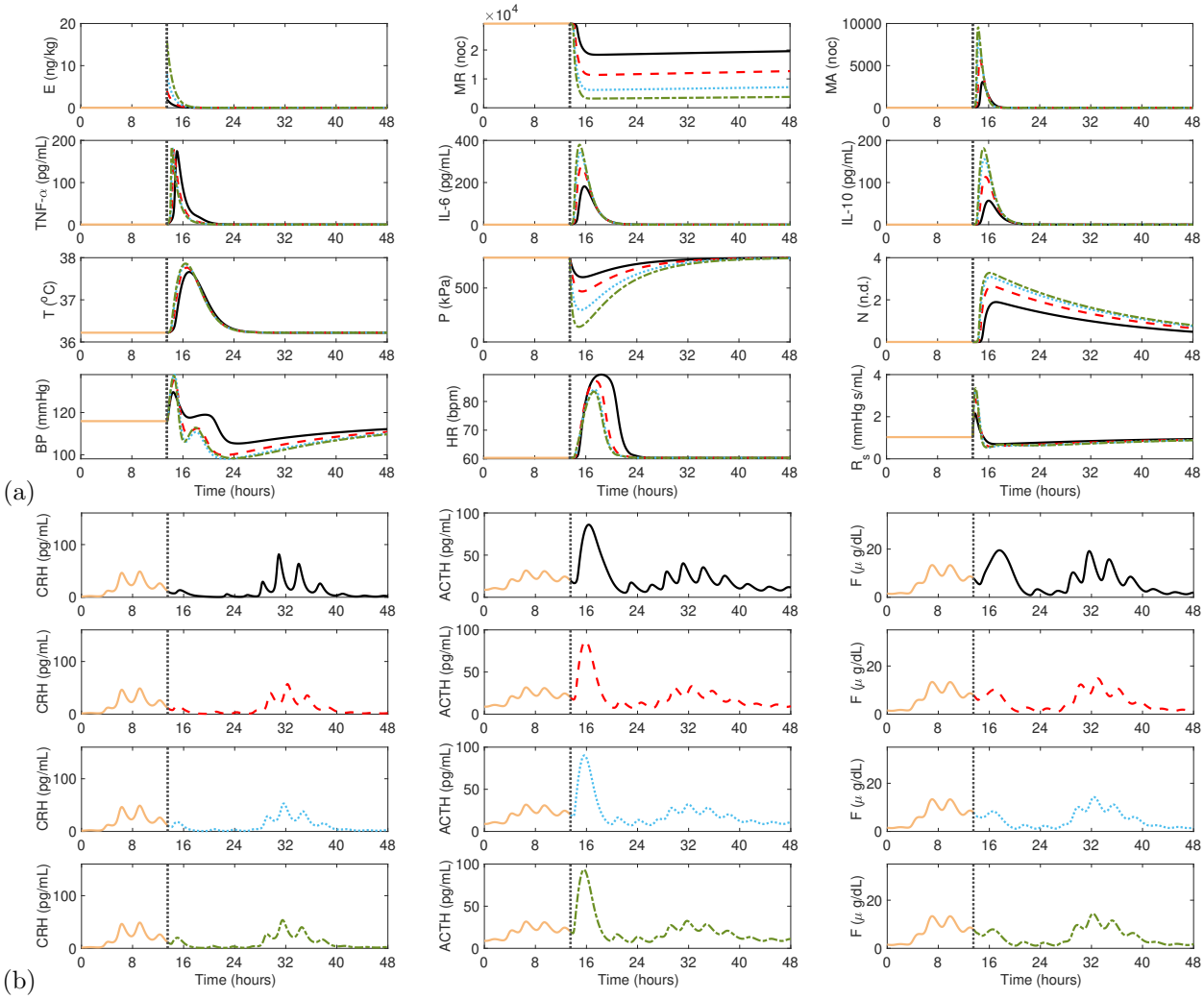


Figure 7: Shortened time course model simulations when the total amount of LPS administered as a bolus dose varies. The solid orange line denotes the model simulation before LPS administration. The vertical dotted line indicates when the LPS was given ($t = 13.5$ hours). Post-LPS model dynamics are shown by solid black lines (2 ng/kg), red dashed lines (4 ng/kg), blue dotted lines (8 ng/kg), and green dashed-dotted lines (16 ng/kg). (a) Inflammatory and cardiovascular simulations. (b) HPA axis simulations.

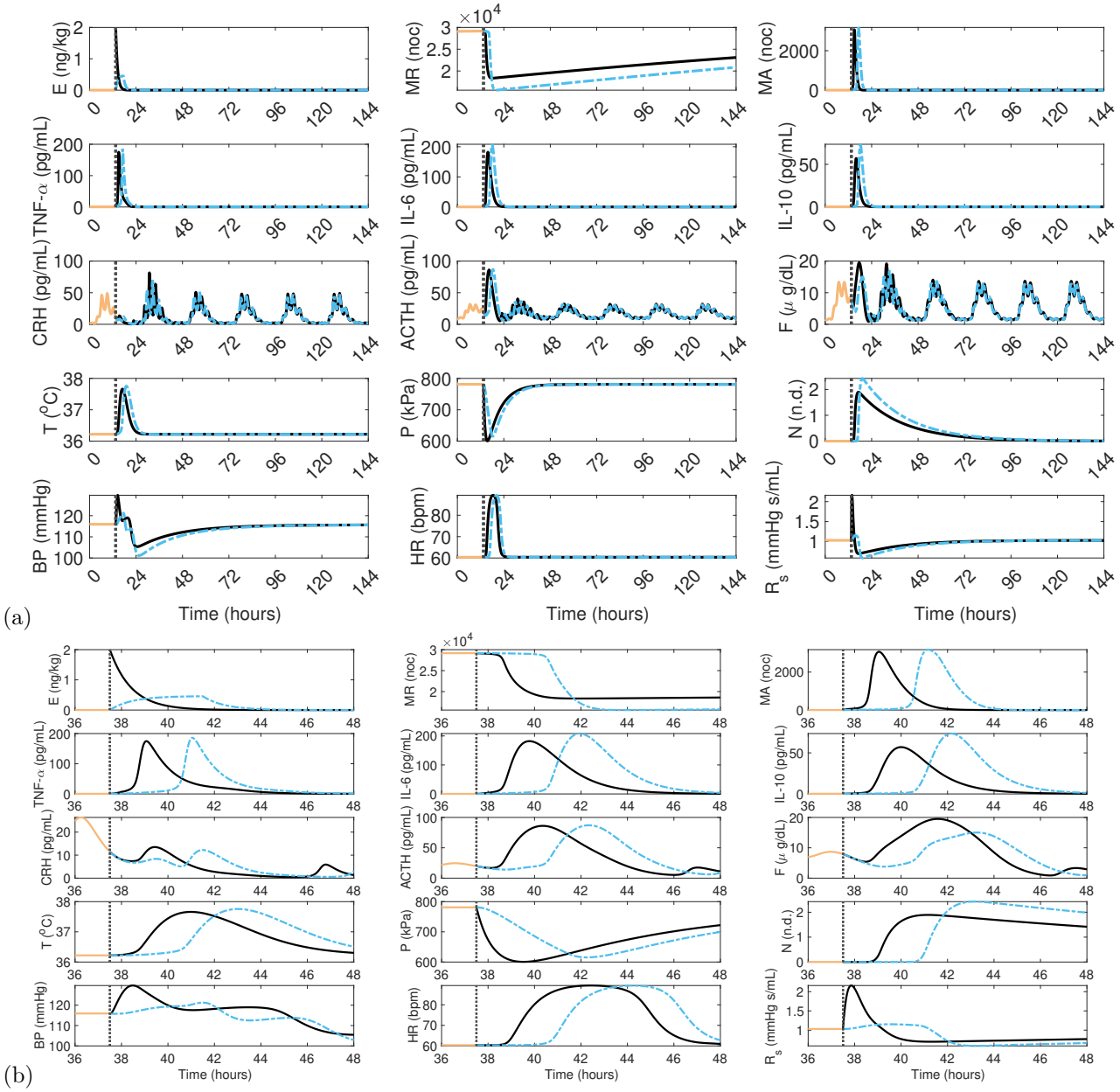


Figure 8: Model simulations for continuous LPS administration. We simulate a 2 ng/kg infusion over 4 hours. The solid orange lines denote results before LPS administration. The vertical dotted lines mark when the LPS is given (at $t = 13.5$ hours). The solid black lines show results for a 2 ng/kg bolus injection, and the dotted blue lines show results with continuous infusion. (a) Extended time course model simulation (six 24-hour cycles). (b) Shortened time course model simulation (half of one 24-hour cycle).