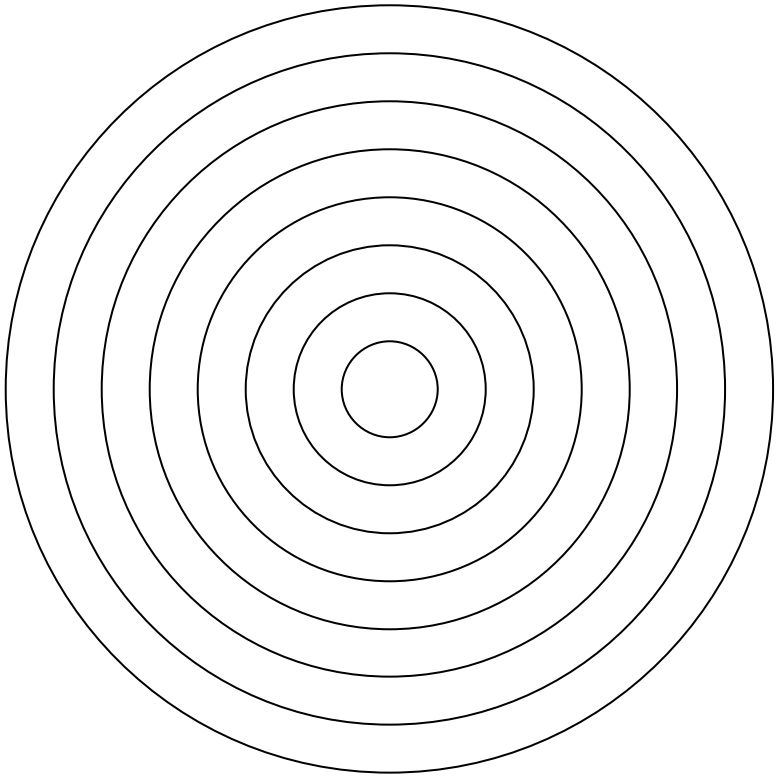
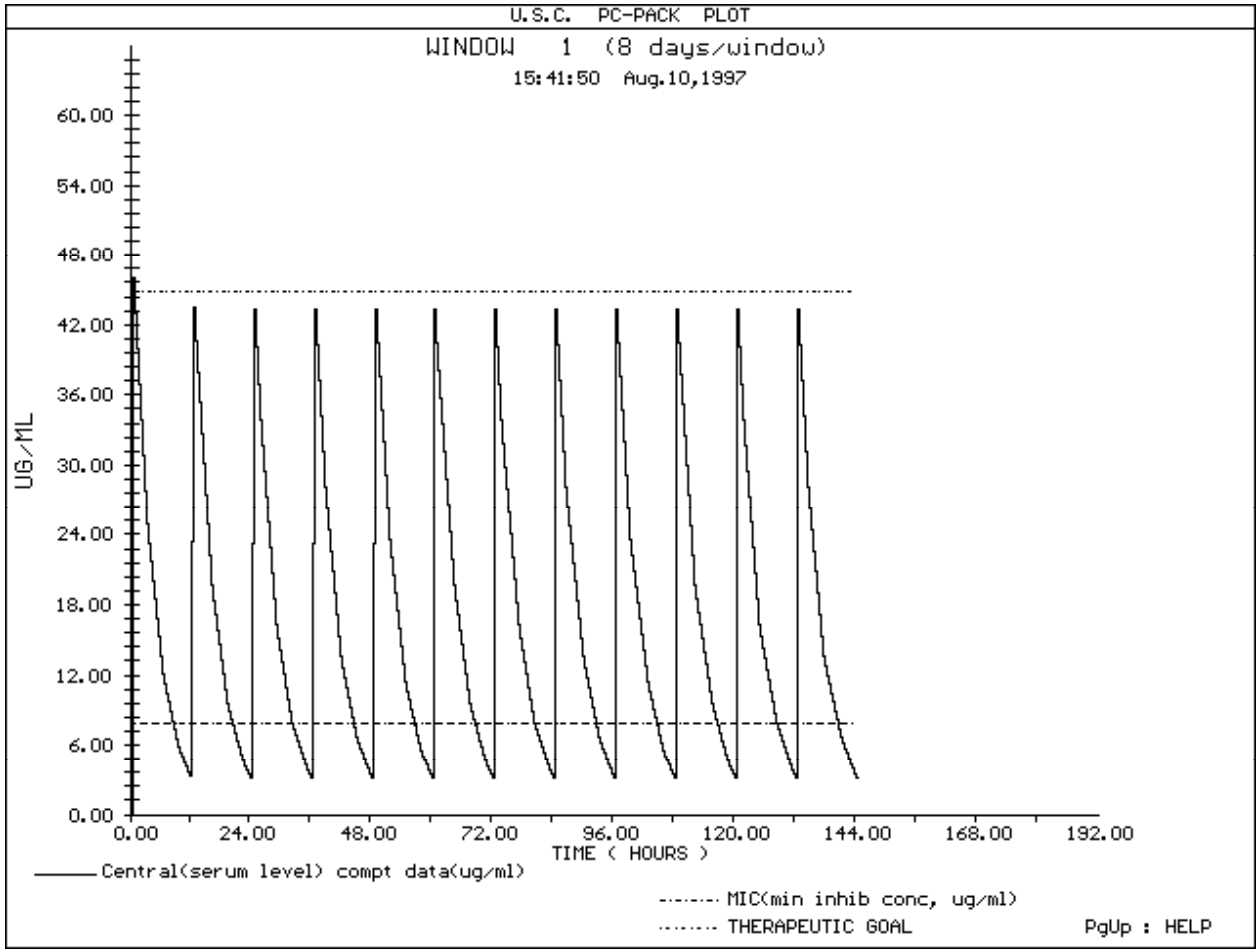
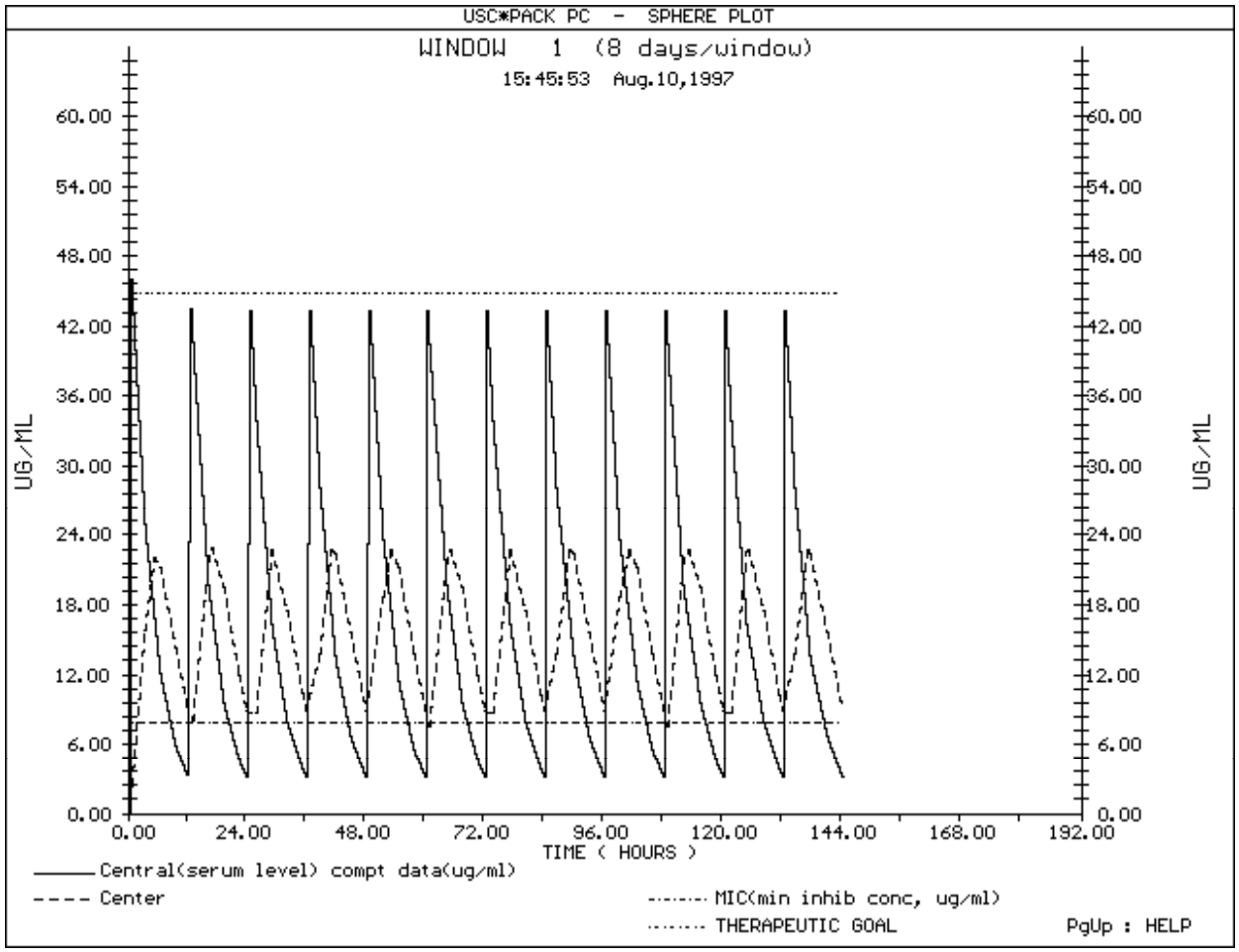
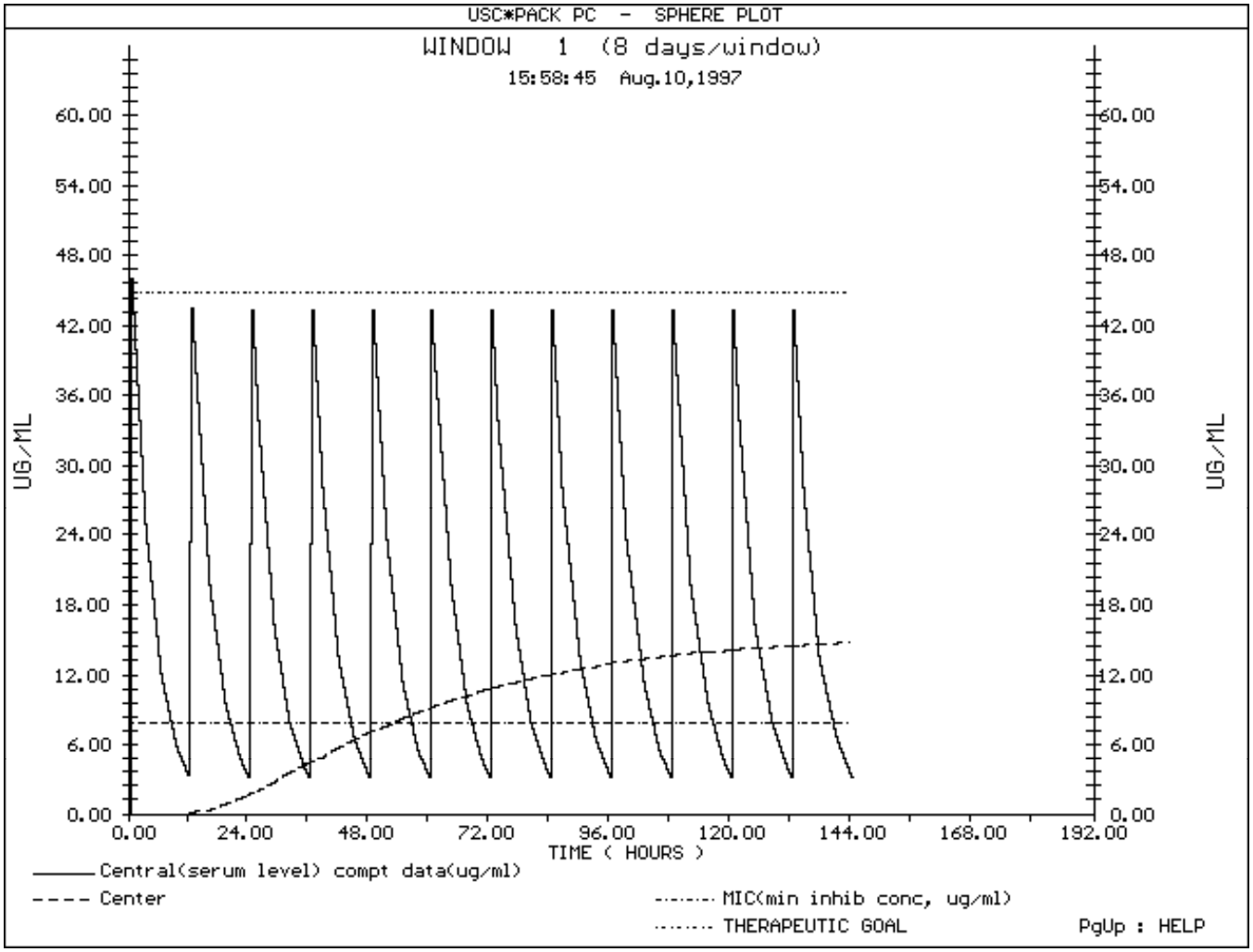




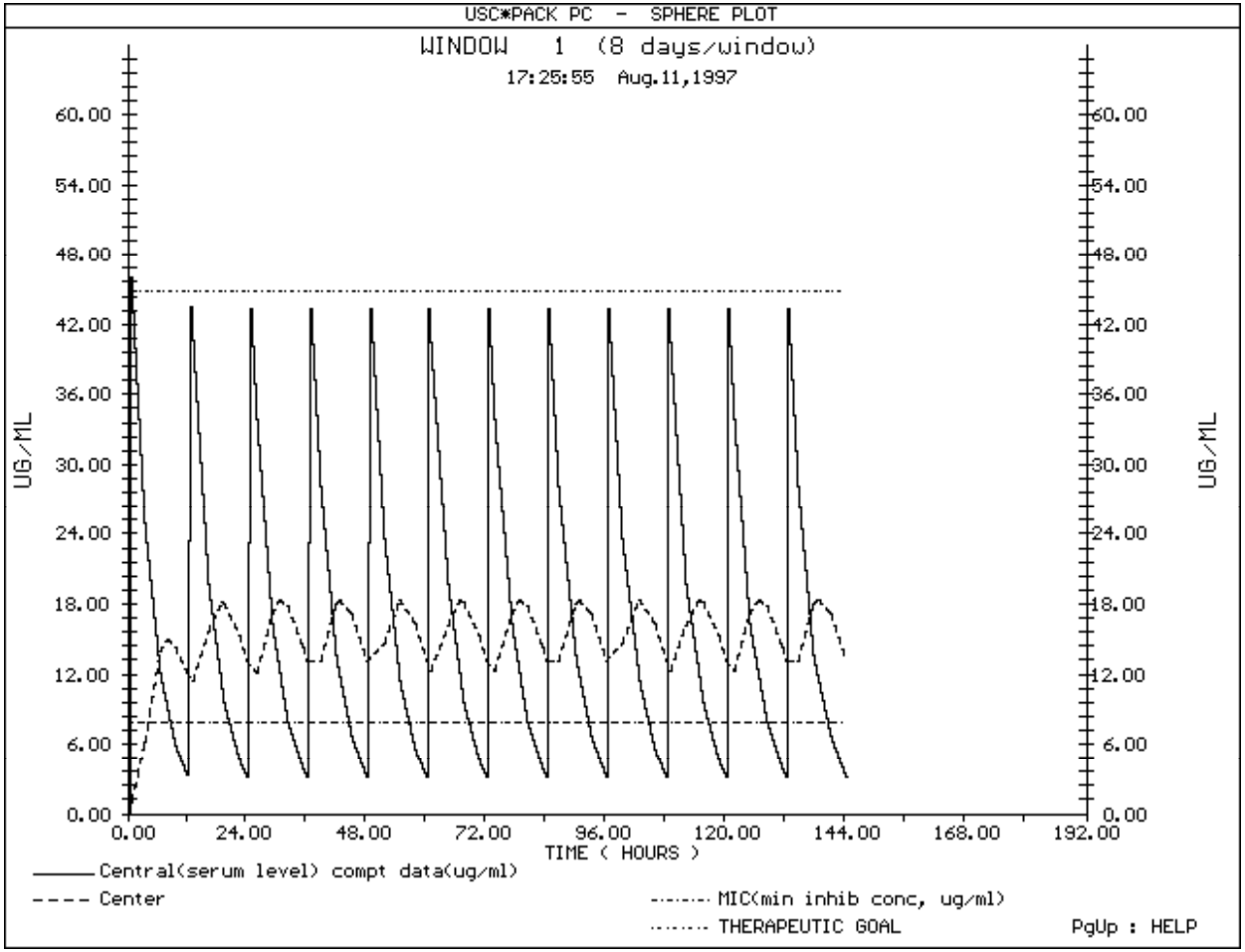
Predicted Time Course (the First 6 Days) of Serum Amikacin Concentrations for the Patient Described. Upper Horizontal Dotted Line - Initial Stated Target Peak Serum Concentration of 45 ug/ml. Lower Horizontal Dashed Line - the Estimated Organism MIC of 8.0 ug/ml.



Predicted time course (the first 6 days) of Amikacin concentrations (dashed line) in the center of a simulated endocardial vegetation of 0.5 cm.



Predicted time course of Amikacin concentrations (dashed line) in the center of a simulated endocardial vegetation of 2.0 cm. The predicted concentrations rise much more slowly and are much more damped, with essentially no oscillations from peak to trough. Once the MIC is reached, the concentrations are consistently above 8.0 ug/ml, but two full days are required before the MIC is reached.



Computed amikacin concentrations in the center of a simulated microorganism. The sphere diffusion model is adjusted so concentrations in the center of the organism lag behind the serum concentrations and fall below the MIC approximately 6 hrs after the serum concentrations, thus simulating a post-antibiotic effect of about 6 hrs.

Modeling Organism Growth and Kill

$$\frac{dB}{dt} = (Kg - Kk) \times B \qquad (1)$$

and

$$Kk = \left(\frac{Emax \times Ct^{n}}{EC50^{n} + Ct^{n}}\right) \qquad (2)$$

B is the relative number of organisms (set to 1 at start of therapy),
Kg is the rate constant for growth,
Kk is the rate constant for killing,
Emax is the maximum possible effect (rate of killing),
EC50 is the concentration at which the killing rate is half maximal,
n is the sigmoidicity coefficient, and
Ct is the concentration at the site of the effect,at any time t.

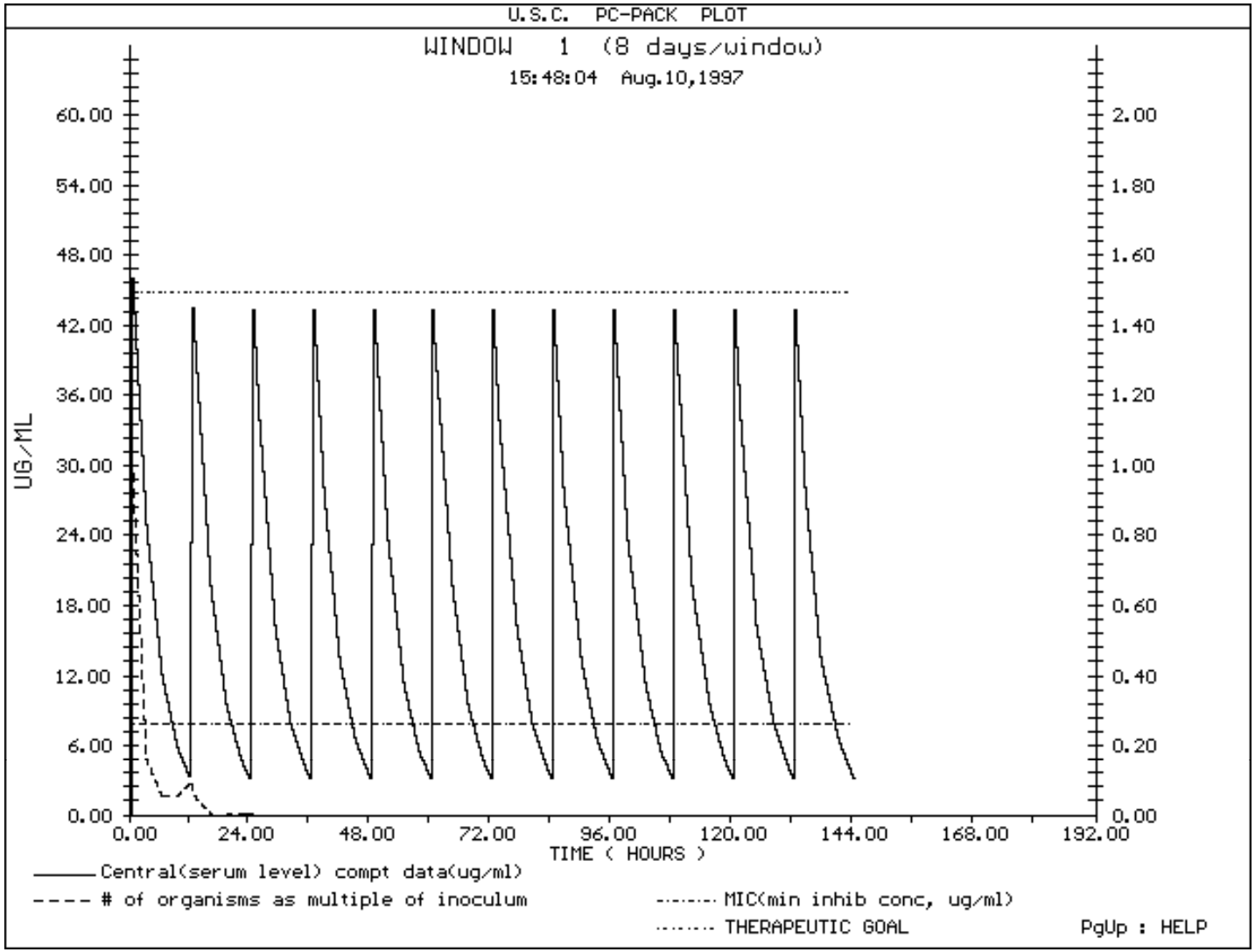
Modeling the Mic and the EC50

$$\frac{dB}{dt} = 0, \quad \text{and } Kk = -Kg \tag{3}$$

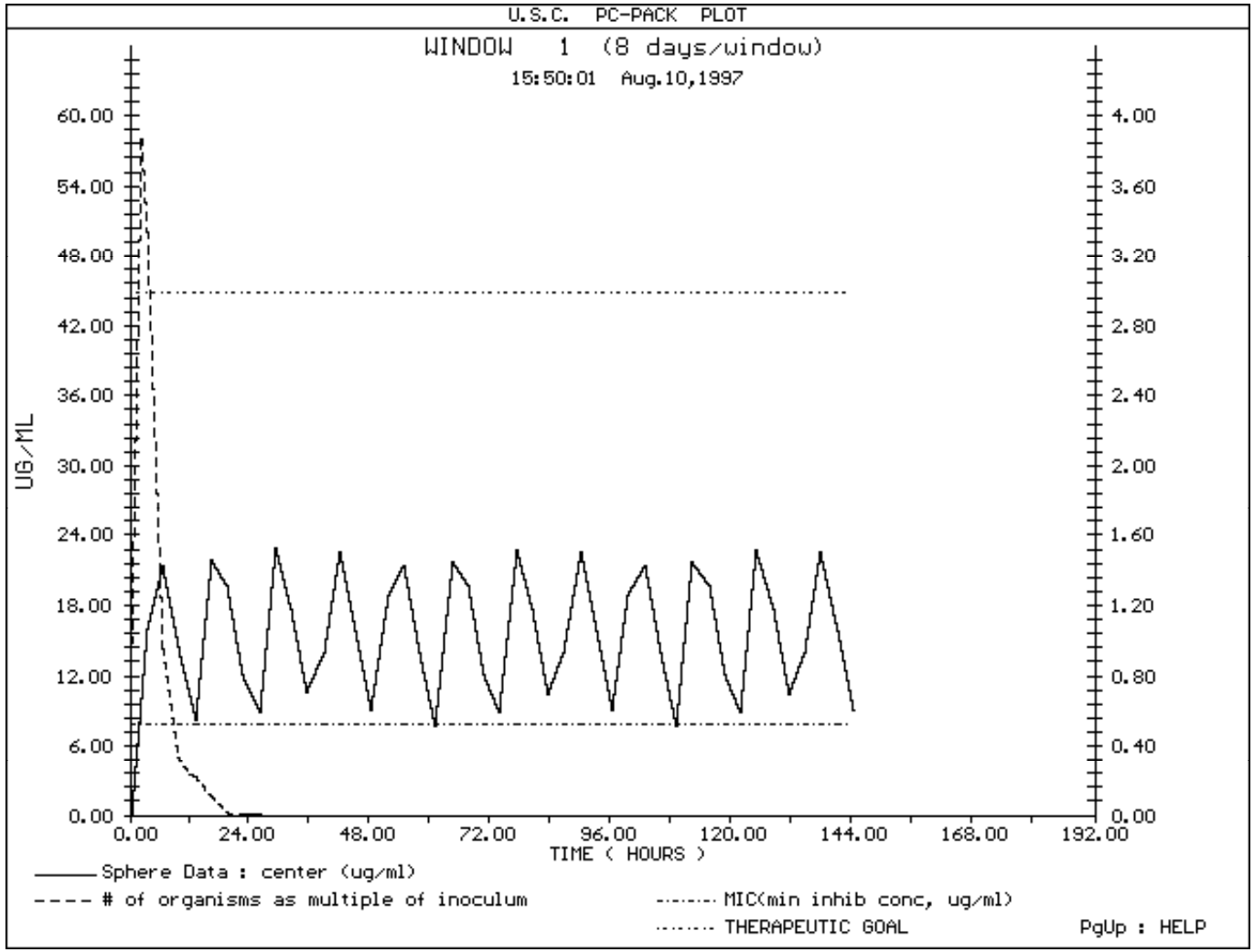
and

$$MIC = \left(\frac{Kg \times EC50^{n}}{Emax - Kg} \right)^{1/n} \tag{4}$$

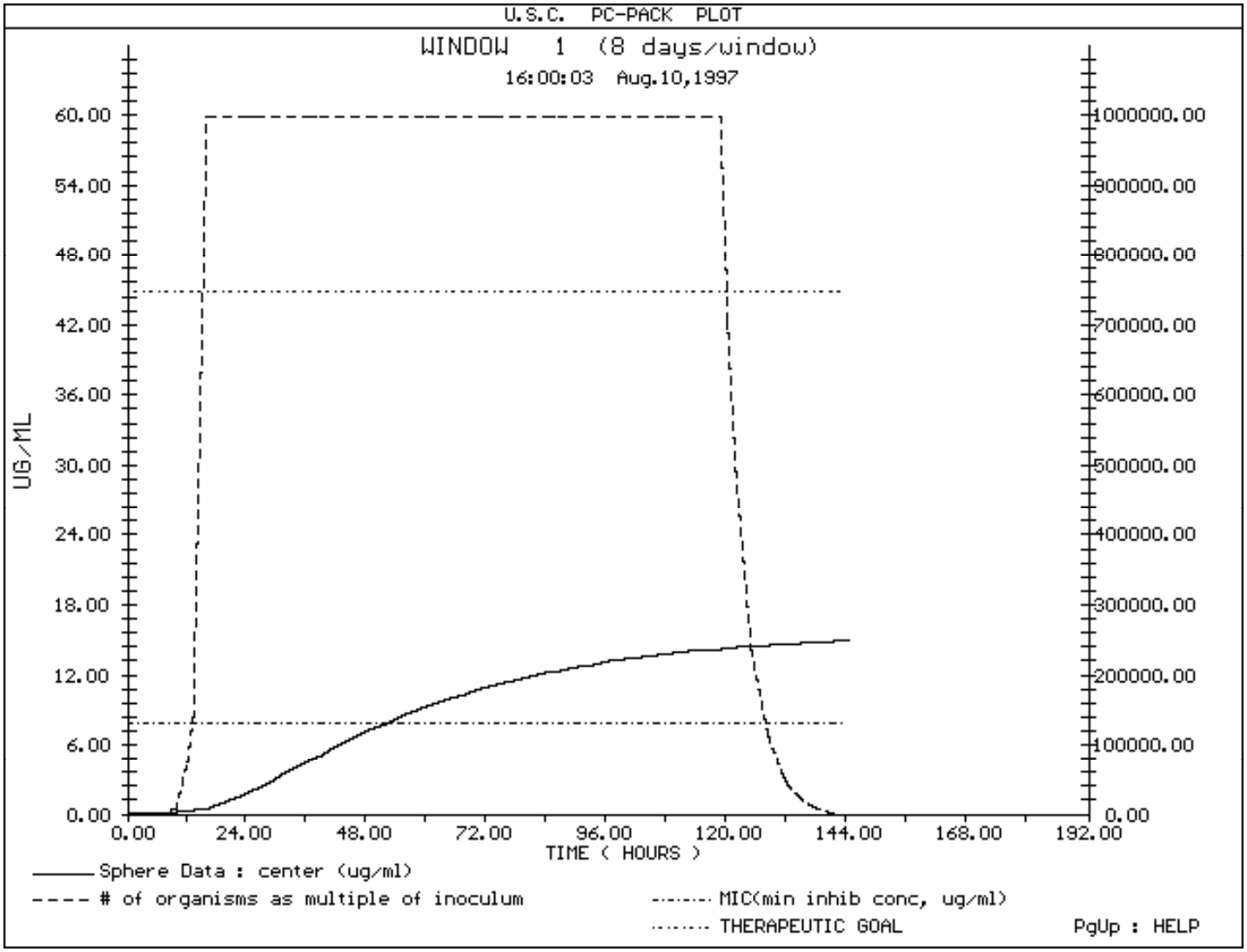
In this way, the EC50 can be found from the MIC, and vice versa.



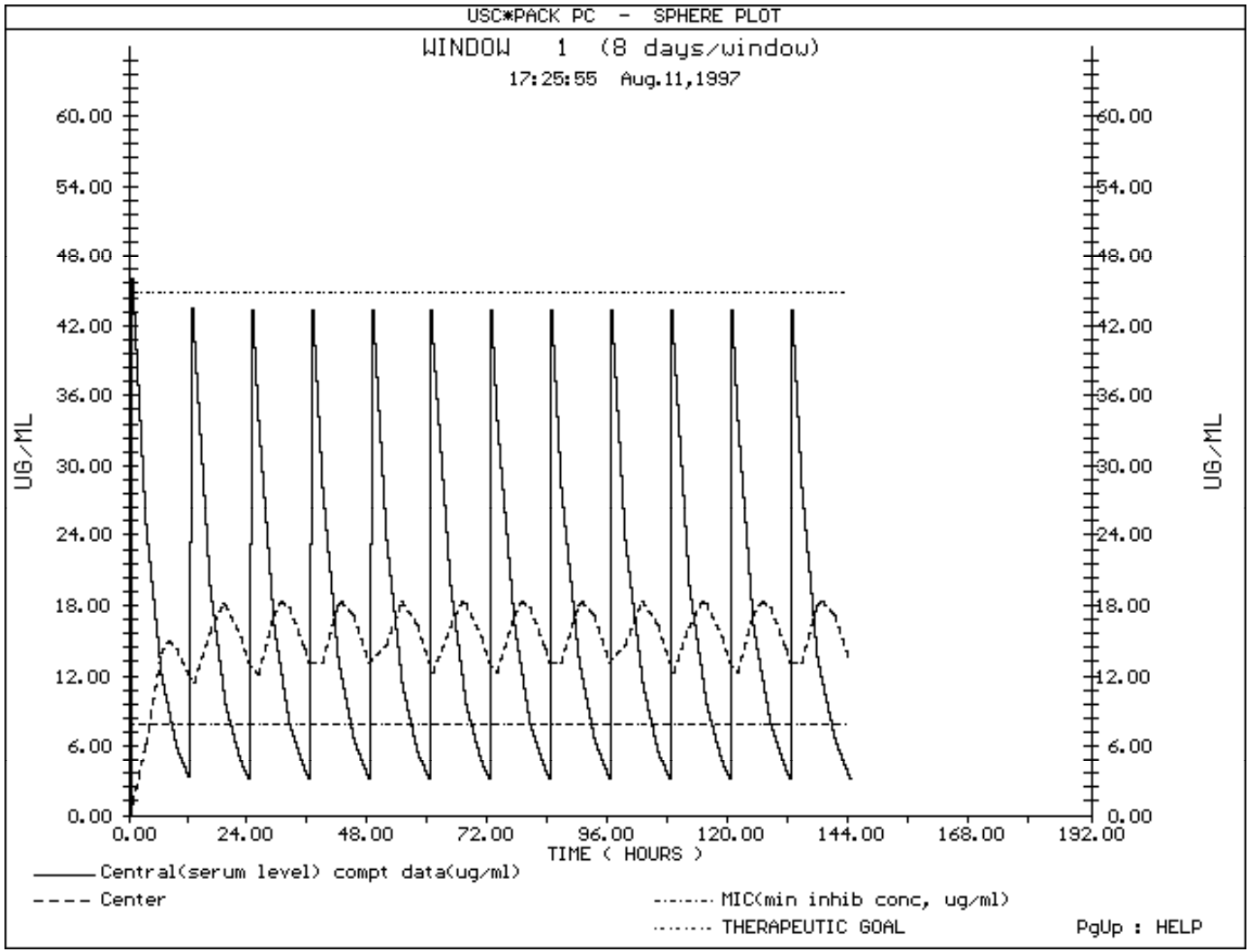
Predicted Killing effect of the regimen. Input from the central (serum) compartment. The regimen is likely to kill well for a bloodstream infection (sepsis). Solid line and left hand scale - serum concentrations. Dashed line and right hand scale - relative numbers of organisms. Upper horizontal dotted and dashed line - original peak serum goal of therapy. Lower horizontal dashed line: patient's MIC of 2.0 ug/ml.



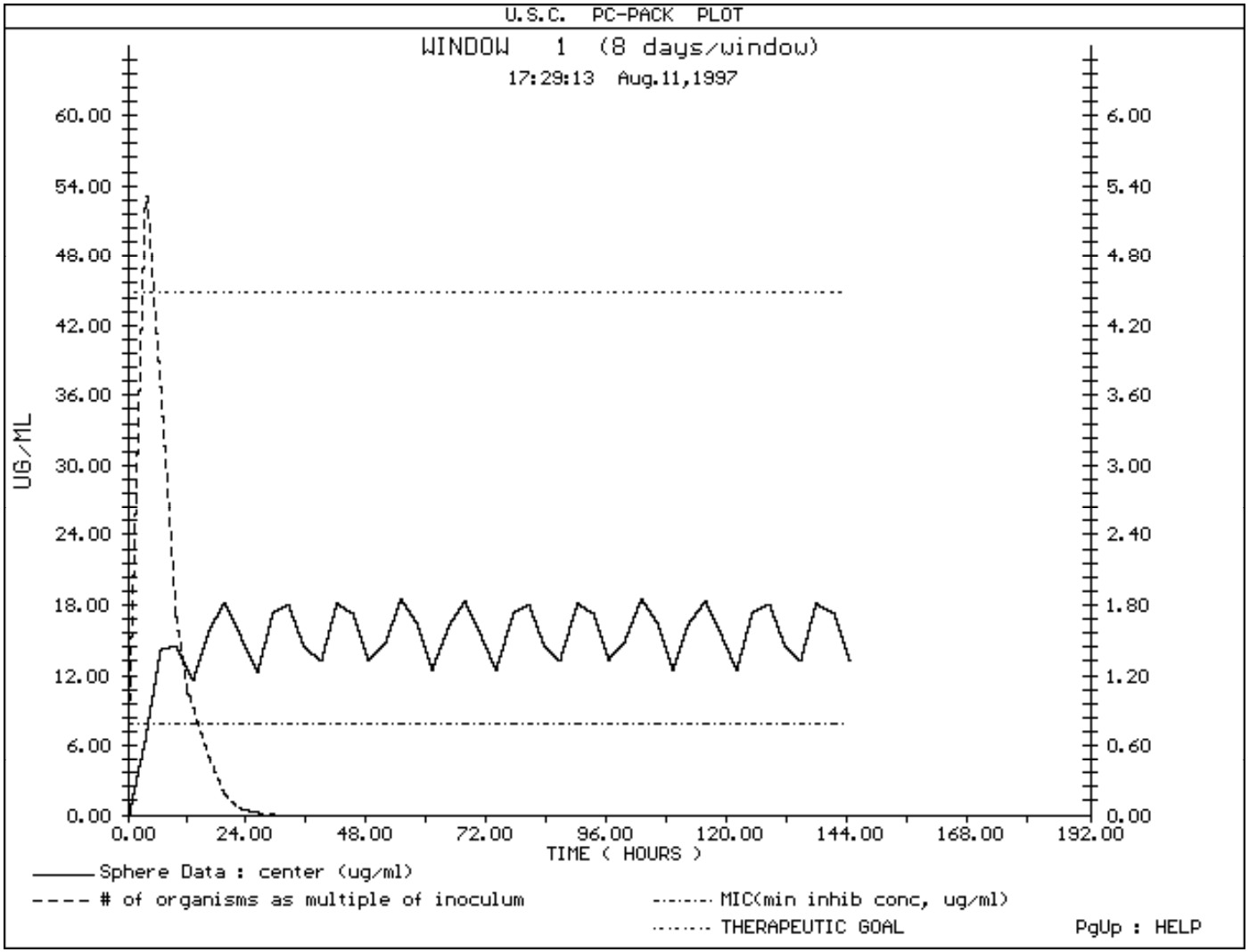
Killing effect predicted in the center of the 0.5 cm diameter vegetation. Good and fairly prompt killing. Solid line and left hand scale - drug concentrations in veg. Center. Dashed line and right hand scale - relative numbers of organisms. Upper horizontal dotted and dashed line: peak serum goal of therapy. Lower horizontal dashed line: patient's MIC of 2.0 ug/ml.



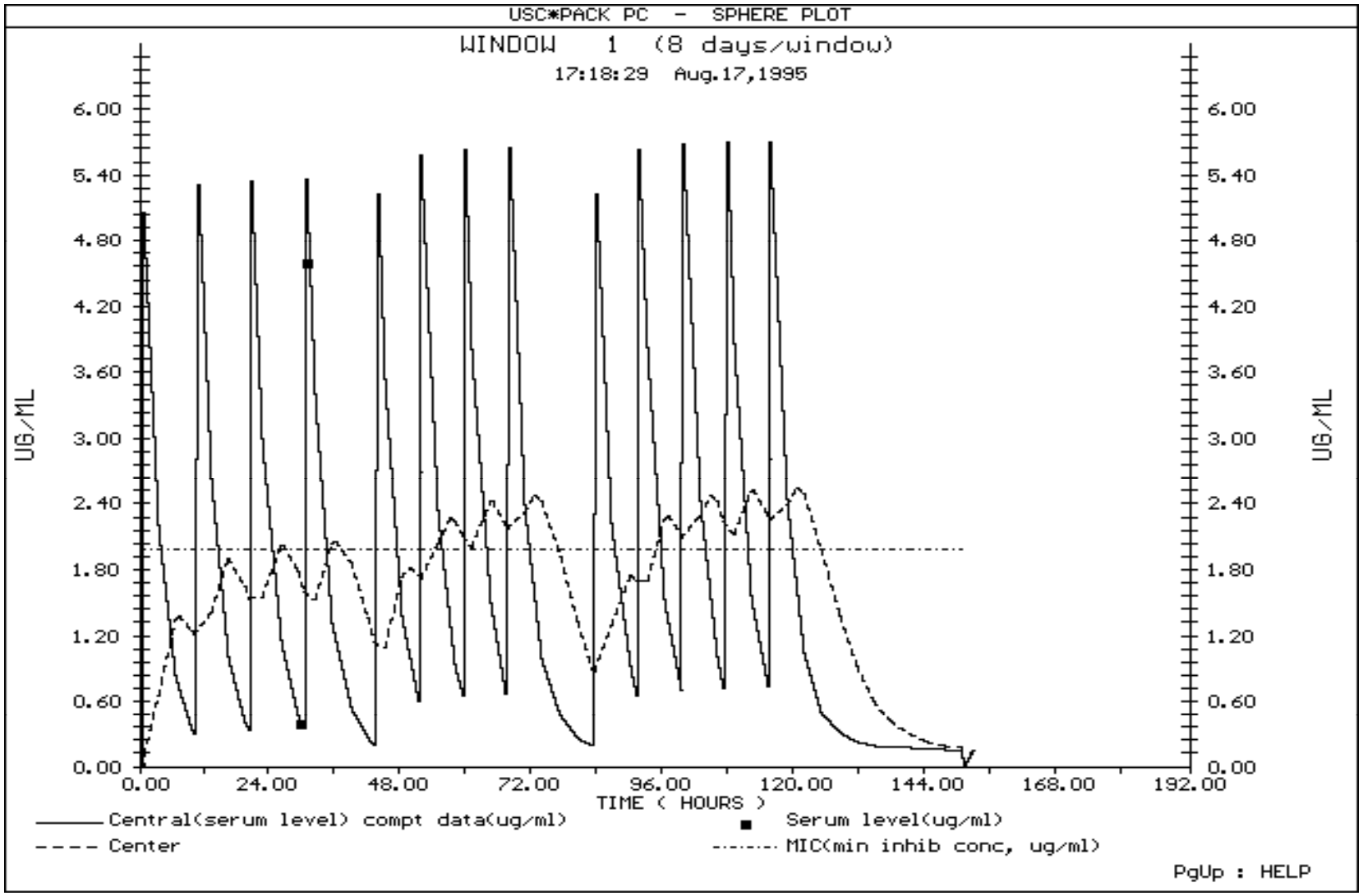
Killing effect in center of a 2.0 cm simulated vegetation. Diffusion is much prolonged. Bacterial growth continues. Killing is delayed. Solid line and left hand scale - drug concentrations in veg. center. Dashed line and right hand scale - relative numbers of organisms. Upper horizontal dotted and dashed line - original peak serum goal of therapy. Lower horizontal dashed line: patient's MIC of 2.0 ug/ml.



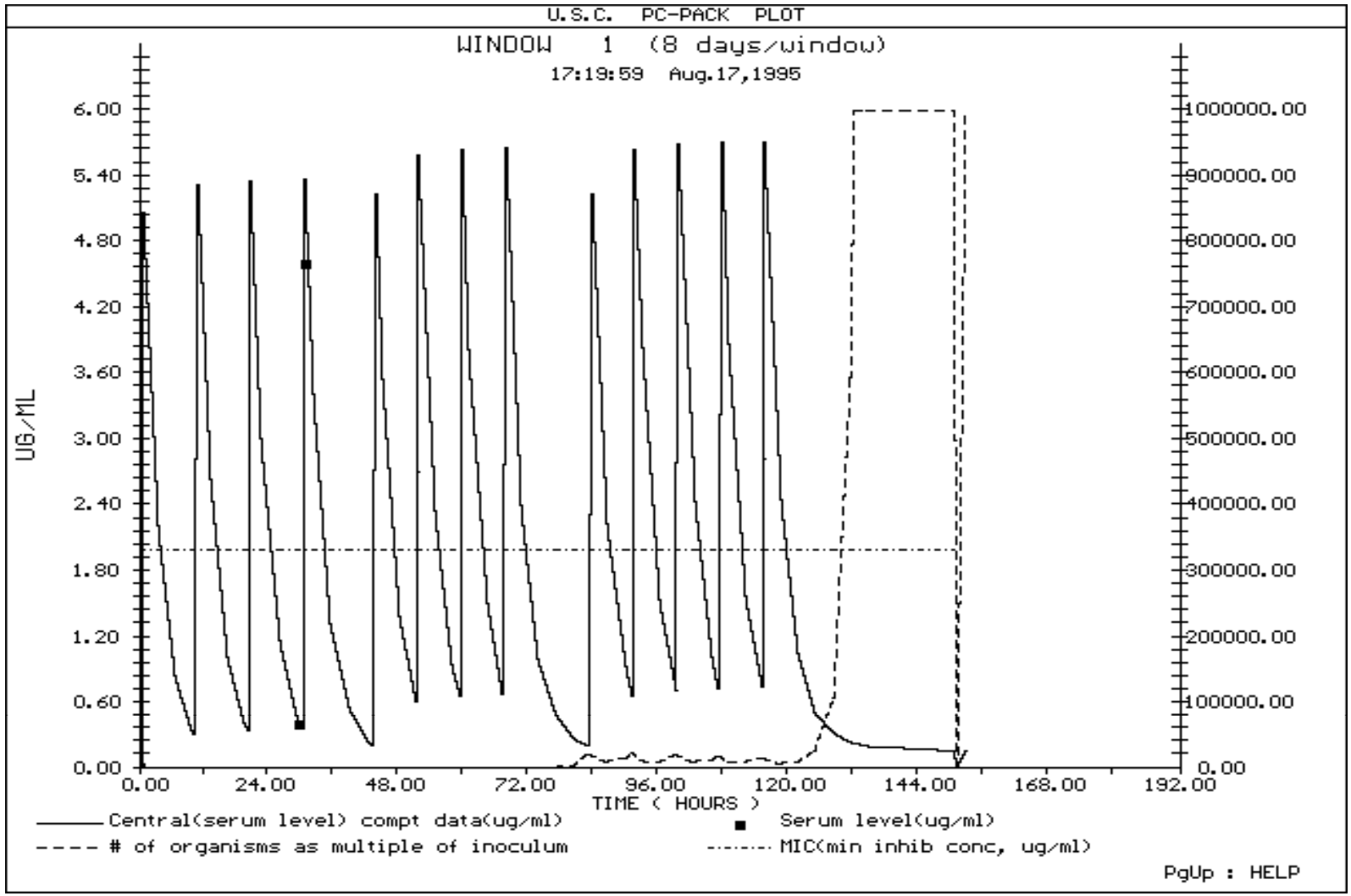
Computed amikacin concentrations in the center of a hypothetical microorganism. Concentrations fall below the MIC about 6 hr after the serum concentrations, simulating (regardless of mechanism) a 6 hr. post-antibiotic effect. Solid line and left hand scale - serum drug concentrations. Dashed line and right hand scale - computed concentrations in the center of the microorganism. Upper horizontal dotted and dashed line - original peak serum goal of therapy. Lower horizontal dashed line: patient's MIC of 2.0 ug/ml.



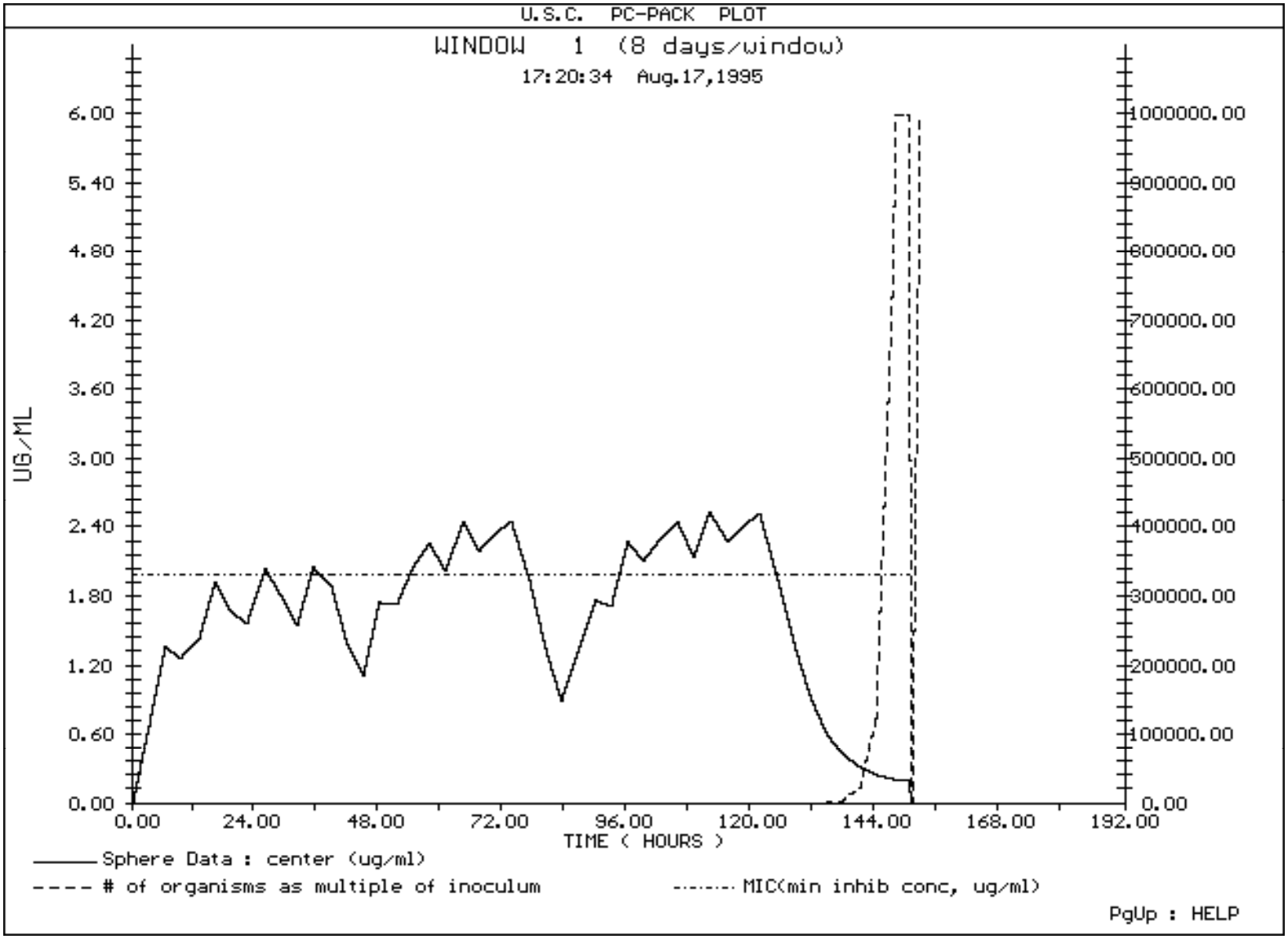
Killing effect for simulated post-antibiotic effect of 6 hrs, using the computed concentrations in the center of the simulated microorganism as input to the effect model. Solid line and left hand scale: drug concentrations in the center of microorganism simulating post-antibiotic effect. Dashed line and right hand scale - relative numbers of organisms. Upper horizontal dotted and dashed line - original peak serum goal of therapy. Lower horizontal dashed line: patient's MIC of 2.0 ug/ml.



Patient receiving Tobramycin. Bayesian fitted model. Small solid rectangles - measured serum concentrations. Solid line and left hand scale - fitted serum drug concentrations. Dashed line and right hand scale - concentrations in organism simulating the post-antibiotic effect. Horizontal dashed line: patient's MIC of 2.0 ug/ml.



Patient on Tobramycin. Measured serum concentrations (small solid rectangles), and pt’s individualized Bayesian fitted model. Solid line and left hand scale: fitted serum drug concentrations. Dashed line and right hand scale: relative numbers of organisms. Plot begins with 1.0 relative units of organism. Horizontal dashed line: patient's MIC of 2.0 ug/ml.



Effects found with model simulating 6 hr PAE. Solid line and left hand scale: drug concentrations in microorganism simulating the post-antibiotic effect. Dashed line and right hand scale: relative numbers of organisms. Horizontal dashed line: patient's MIC of 2.0 ug/ml