INTRODUCTION:
Systemic exposure has been measured for antibiotic impregnated acrylic bone cements. It is not possible, however, to experimentally determine the drug concentration in the local bone tissue of humans. This greatly inhibits our understanding of the mechanisms at play for antibiotics in the target tissue, such as time above minimal inhibitory concentrations (MIC). Physiologically based pharmacokinetic (PBPK) models are a powerful tool and provide insight into the disposition of drug in the body. A physiologically based mathematical model was developed for antibiotic bone cement to simulate the local concentration of tobramycin delivered to the acetabulum and the concentration in systemic circulation. Simplex™ P with Tobramycin is indicated for the fixation of prostheses to living bone for use in the second stage of a two-stage revision for total joint arthroplasty in the US, and it is indicated as a bone cement in prosthetic surgery in Europe and Australia.

METHODS:
The simulations were performed using a purpose-built mathematical model with the technical computing software MATLAB® (The MathWorks, Inc. Natick, MA). As shown in Figure 1, each of the key organs in the human body were simulated with coupled ordinary differential equations describing the volumes, inflows, outflows and partitioning of drug. All physiological parameters for the model were determined from the physiologically based pharmacokinetic literature. The model was then customized according to the IV parameters for tobramycin.

As shown in Figure 2, a key aspect of the PBPK model is the interface between the cement surface and the bone tissue. The specific geometry of the cement was modeled using time dependent diffusion equations to simulate the drug release. The output from this sub-compartment was then interfaced with the model as shown by the blue box in Figure 1.

RESULTS
Reference 1 provided patients’ systemic serum concentrations after undergoing a total hip arthroplasty with antibiotic bone cement. This data was input into the model, and Figure 3 shows the results of the simulations. In this figure, the inset is the measured (circles) and simulated (curve) concentration of tobramycin in the systemic circulation. Based on the systemic data and the model, the behavior of the released drug from bone cement can be inferred. The concentration of tobramycin in the acetabulum is shown in the blue curve. The simulation results show that the concentration of tobramycin in the tissue adjacent to the implant is approximately 30-fold higher than the systemic blood levels.

DISCUSSION:
The simulations for the release of tobramycin from bone cement show excellent agreement with the systemic concentration as a function of time. Given that the model is trained with IV data to accurately simulate the disposition of tobramycin, this result suggests that the assumptions regarding the release of drug from the implant into the bone are reasonable. This model is a predictive tool that can be used to help understand the local delivery of antibiotics from bone cement and the potential for local efficacy against bacteria.

REFERENCES: