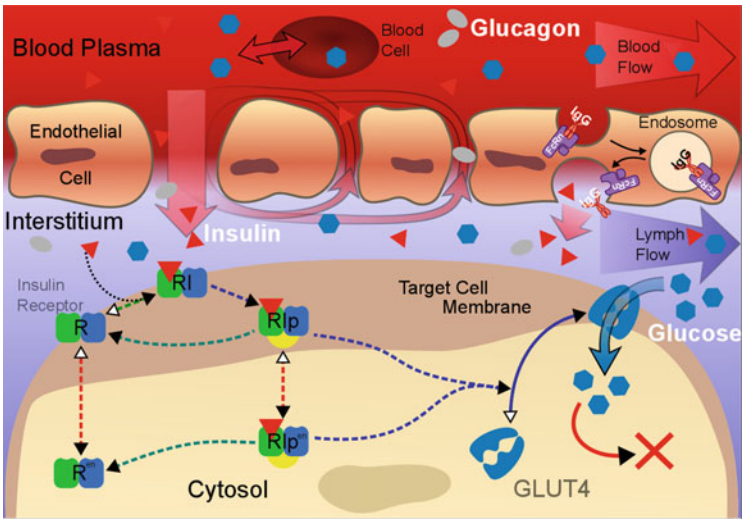

Fig. 4 Sub-organ-level and molecular details represented: organs are represented by five sub-compartments (blood plasma and cells, endothelial endosomes, interstitial, intracellular). Compartments are connected by passive convection, diffusion, and facilitative transports. Distribution of compounds depends on concentration gradients, flow rates, permeability, partition coefficients, transporter properties, and target protein-binding properties. Insulin distribution and its glucoregulatory effects are mediated by insulin receptor (IR)-mediated elimination from the plasma and interstitial space through *trans*-endothelial transport and cellular uptake which triggers molecular signaling in target tissues. Downstream signaling of the insulin receptor in fat and muscle triggers translocation of insulin-sensitive glucose transporter GLUT4, increasing peripheral glucose uptake (figure modified from Schaller et al. 2013)

kinetic constants of transport process, etc. Then, a mean model representing typical behavior under standard glucose and insulin tolerance tests was developed. Parameters were divided into three groups. The first group consists of the parameters assumed to be identical for all volunteers and patients. The second group distinguishes healthy subjects and type 1 diabetics (T1DM) and the third group distinguishes individuals in each group.

The model was then further developed using published clinical trial data with glucose, insulin, and glucagon concentration-time curves at high temporal resolution. El-Khatib and colleagues (2010) studied T1DM patients over several hours and densely sampled all three analytes while they performed insulin, glucose, and glucagon challenges (Fig. 5). The data allowed the adjustment of patient-specific models representing the dynamic responses of the patients to exogenous challenges and meals. A comparison between experimental data and simulated model responses shows an excellent match (Fig. 5).

For each patient, El-Khatib and colleagues repeated the experiment which allowed a rigorous test of the predictive performance of the individualized models. Figure 6 shows a comparison between experimental data and the predicted time