



Figure S1. Architectural layers and components of the NeoRelief system.

This is a modular system which allows the reuse of certain components in different services and applications; higher layers are dependent on lower layers.

- The bottom level represents a library of objects describing fundamental PKPD processes like absorption, distribution, metabolism and effect (ADME). These objects, which implement the fundamental PKPD equations, can be combined to create a PKPD model. The Edsim++ application has a visual model designer interface for this task.
- The next layer is called the PKPD framework. Here actual calculation tasks are performed with the model (simulation, fitting and dosing).
- The top layer on the left represents the Edsim++ application layer which is associated with a graphical user interface. Edsim++ deals with general purpose PKPD modeling, but new specialized functionality can be added to the Edsim++ application by means of so-called plug-ins. The MwPharm++ plug-in adds drug monitoring capabilities to Edsim++. The NeoRelief++ plug-in represents our stand-alone test and demonstration environment used for helping in the development of the Epic web version of NeoRelief.

NeoRelief++ and NeoRelief do not directly communicate with the Edsim++ PK-Engine. An intermediate layer was created (NeoServer), which contains specific knowledge related to morphine precision dosing. Also, the application programming interface (API) of the NeoServer layer is much simpler than the API of the PK-Engine. So, the NeoServer layer shields Epic developers from the complexity of PKPD-modeling.

The NeoServer logic is made available as a web service by the NeoWebApi layer. This is a communication layer that does not contain any business logic on its own. NeoRelief follows the micro services paradigm, in which a precision dosing service for different drugs can be implemented as their independent micro service which can be used by different applications at the same time.