Rapid quantitative pharmacodynamic imaging with Bayesian estimation

Jonathan M. Koller[1], M. Jonathan Vachon[2], G. Larry Bretthorst[3], and Kevin J. Black[4]

[1]**Department of Psychiatry, Washington University in St. Louis, St. Louis, MO, United States**
[2]**College of Arts & Sciences, Washington University in St. Louis, St. Louis, MO, United States**
[3]**Department of Radiology, Washington University in St. Louis, St. Louis, MO, United States**
[4]**Departments of Psychiatry, Neurology, Radiology, and Anatomy & Neurobiology, Washington University in St. Louis, St. Louis, MO, United States**

ABSTRACT

We recently described rapid quantitative pharmacodynamic imaging, a novel method for estimating sensitivity of a biological system to a drug. We tested its accuracy in simulated neuroimaging signals with varying receptor sensitivity and varying levels of random noise, and presented initial proof-of-concept data from functional MRI (fMRI) studies in primate brain. However, the initial simulation testing used a simple iterative approach to estimate pharmacokinetic-pharmacodynamic (PKPD) parameters, an approach that was computationally efficient but returned parameters only from a small, discrete set of values chosen *a priori*.

Here we revisit the simulation testing using a Bayesian method to provide more accurate estimates of the PKPD parameters. This produced improved accuracy, and noise without intentional signal was never interpreted as signal. This approach improves the ability of rapid quantitative pharmacodynamic imaging to reliably estimate drug sensitivity (EC_{50}) from simulated data. The success with these simulated data paves the way for analyzing experimental data acquired for rapid quantitative pharmacodynamic imaging to validate it against results obtained by traditional methods in the same subjects.

Keywords: Pharmacodynamics, Pharmacokinetic-pharmacodynamic modeling, Drug development, Dose-finding, EC_{50}, phMRI, Pharmacological fMRI, ED_{50}, Bayesian parameter estimation, fMRI

INTRODUCTION

Measuring the sensitivity of an organ to a drug *in vivo* is a common, important research goal. The traditional approach is to independently measure biological responses to a range of different doses of drug. We recently described a novel method, rapid quantitative pharmacodynamic imaging (or QuanDyn™), for estimating sensitivity of a biological system to a drug in a single measurement session using repeated small doses of drug (Black et al., 2013). In that report we tested QuanDyn™'s accuracy in simulated data with varying receptor sensitivity and varying levels of random noise. The initial simulation testing used a simple iterative approach to estimate pharmacokinetic-pharmacodynamic (PKPD) parameters including EC_{50}, the plasma concentration of drug that produces half the maximum possible effect E_{max}. The iterative approach was computationally efficient but could only select EC_{50} from a short list of parameter values chosen *a priori*. Here we revisit the simulation testing using a Bayesian method to provide continuous estimates of the PKPD parameters. The Bayesian approach also identifies data too noisy to produce meaningful parameter estimates.

METHODS

Simulated data

We used a standard PKPD model to create 6 time-effect curves that could reasonably represent BOLD signal from a pharmacological challenge fMRI study: one with no response to drug ($E_{max} = 0$) and five with varying sensitivities to drug: $E_{max} = 10$ and $EC_{50} \in \{0.25, 0.6, \sqrt{2}, \pi, 7.5\}$.

As in the previous work, the concentration of drug in plasma over time is modeled as

$$C(t) = \sum_{k=1}^{K} D_k \cdot u(t - t_s - t_k) \cdot 2^{-(t-t_s-t_k)/t_{1/2}}$$

where K doses of drug, D_k, are given at times t_k, $u(t)$ is the unit step function, t_s (for "time shift") is a fixed delay between drug concentration and effect, and $t_{1/2}$ is the elimination half-life of drug from plasma (Black et al., 2013). Drug effect is modeled as

$$E(C) = \frac{E_{max} C^n}{(EC_{50})^n + C^n}$$

where C is $C(t)$ from the previous equation and n represents the Hill coefficient. Nonquantitative signal drift typically encountered with BOLD-sensitive fMRI was simulated by adding to each curve a quadratic function of time $a_0 + a_1 t + a_2 t^2$. These test curves were generated using $K = 4$, $D_1 = D_2 = D_3 = D_4 =$ the dose of drug that produces a peak plasma concentration of 1 (arbitrary concentration units), $t_s = 0.5$ min, $t_{1/2} = 41$ min, $n = 1$, $a_0 = 1000$ (a typical value from brain in our lab's BOLD analysis pipeline), $a_1 = 2t/(40min)$, and $a_2 = 0$. The 6 resulting curves are shown in Figure 1.

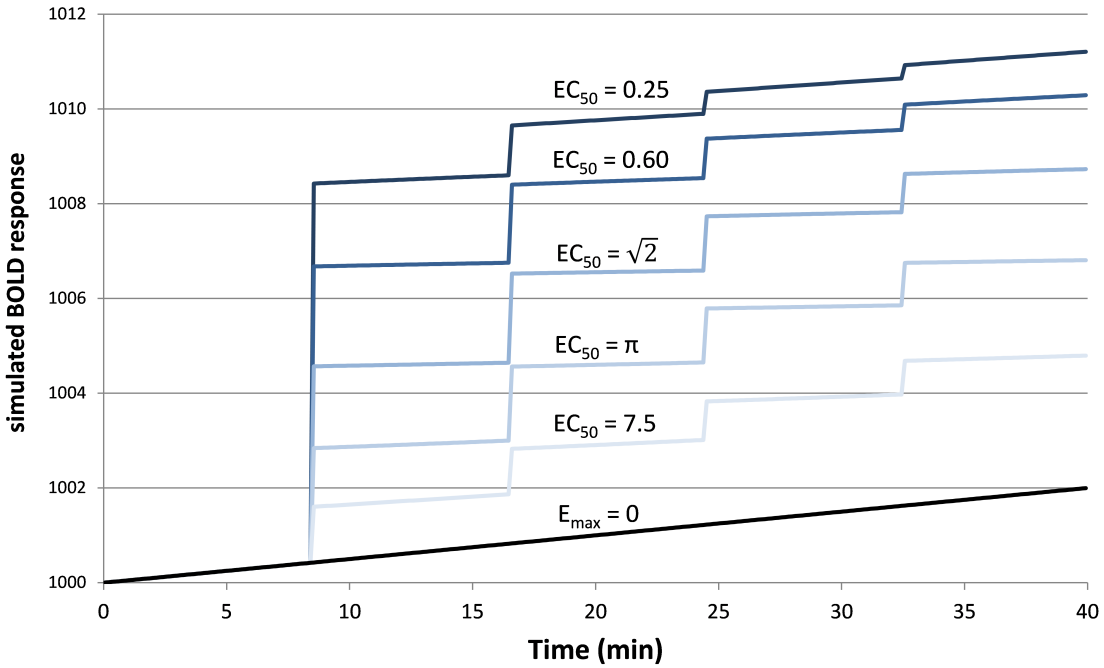

Figure 1. Test data for different levels of EC_{50}.

Finally we added Gaussian noise to each time point. This was done 1000 times for each of the 6 curves above and for each of 8 noise levels from $SD = 0.01E_{max}$ to $2E_{max}$, resulting in 48,000 noisy time–signal curves plus the original 6 "clean" curves (see Supplemental Data).

Testing the method using the simulated data

In the simulated fMRI test data described above, each of the 48,006 time courses was analyzed using the Bayesian Data-Analysis Toolbox (Bretthorst and Marutyan, 2014). The Toolbox implements a Markov chain Monte Carlo (McMC) method for analysis of a variety of problems including parameter estimation across 4d images (Bretthorst, 1988; Bretthorst and Marutyan, 2014). This analysis was performed with the Image Pixels Model Selection package, which uses Bayesian probability theory to determine which model better accounts for each set of data. Here the package returns a quantitative estimate of the probability p that the full PKPD model described above accounts for the given data set better than a simpler model consisting only of $a_0 + a_1 t + a_2 t^2$. If $p > 0$, the package also returns the values for EC_{50}, t_s, E_{max}, a_0, a_1, and a_2 that best fit the data given the PKPD model.

To provide more even sampling of parameter space across the conventional logarithmic abscissa for concentration-effect curves, EC_{50} was coded as 10^q, where $q = \log_{10} EC_{50}$, and a uniform prior probability was assumed for q with range $[-3, 1.3]$, corresponding to EC_{50} values from 0.001 to 20.0. A uniform prior with range 0-1min was used for the time shift parameter t_s. The Hill coefficient n and the drug's elimination halflife—parameters that for biological data could be estimated separately, from a typical PK study—were fixed at $n = 1$ and $t_{1/2} = 41$ minutes. E_{max} and the coefficients of the signal drift function $a_0 + a_1 t + a_2 t^2$ were marginalized.

Since tissues with high values of EC_{50} respond less to a given dose of drug, *i.e.* $E \ll E_{max}$, the ratio $SD/E_{max} \ll SD/E$ underestimates the effect of noise relative to the observed effect. Therefore we computed a signal-to-noise ratio (SNR) to simplify comparisons across the various input values of EC_{50} and noise. We defined "signal" as the maximum value of $E(C(t))$, without added noise, for $0 \leq t \leq 40$min, *i.e.* the local maximum of the modeled signal shortly after the last dose of drug, less the input linear drift at that same time point. In Figure 1 this value can be appreciated near the right side of the plot and ranges from about 3.5 for $EC_{50} = 7.5$ to about 9.5 for $EC_{50} = 0.25$. We define SNR as the ratio of this signal by the standard deviation of the added noise.

RESULTS

Example

Figure 2 provides an example result from one time course, to orient the reader to the following summary. Note that the parameter estimates are (approximately) the best estimates to the provided noisy data, even though they differ slightly from the input values used to produce the data.

Sensitivity: p(model) with signal

The full PKPD model explained the data better than a simpler model, *i.e.* p(model) >0.5, except when signal was low (higher EC_{50}) or noise was substantial (Figures 3, 4).

False positives: *p*(model) with noise only

For the images containing no intentional signal, *i.e.* noise added to the $E_{max} = 0$ line, the Toolbox never returned $p > 0.5$ for any of the 8,000 voxels. In other words, there were no false positives.

Accuracy

Accuracy of the EC_{50} estimate was considered for time courses with p(model) >0.5. Figure 5 shows the mean estimated EC_{50} as a function of the input EC_{50}; as expected, accuracy is best with higher SNR. Figure 6 shows the ratio of estimated EC_{50} to input EC_{50} in terms of SNR. Perfect accuracy would produce a ratio of 1.0, and values >1.0 indicate overestimation of EC_{50}, *i.e.* underestimation of the sensitivity to drug.

DISCUSSION

Bayesian parameter estimation for the QuanDyn^{TM} quantitative pharmacodynamic imaging method produces excellent results. The Model Select method very accurately identified time courses with a meaningful drug-related

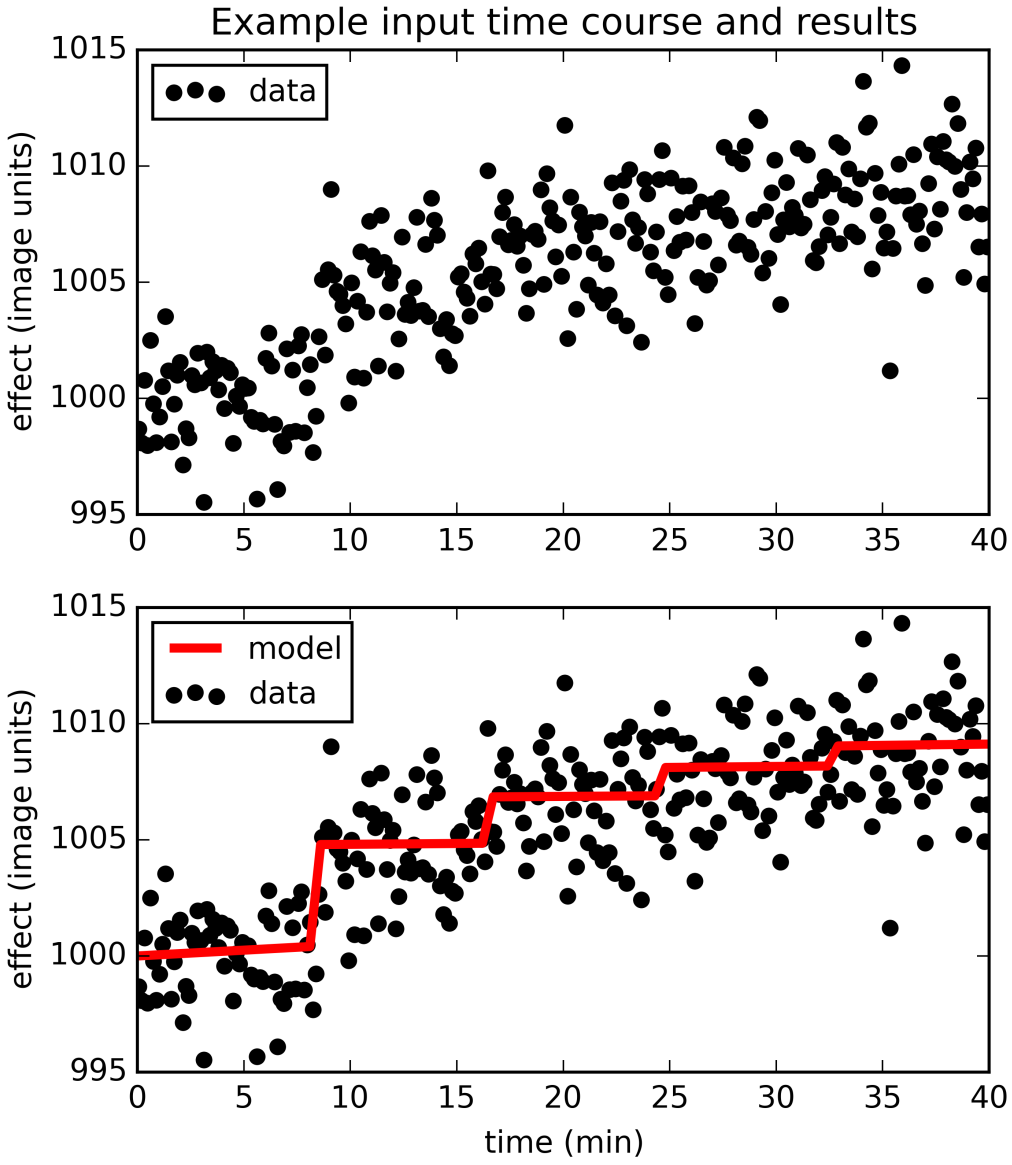

Figure 2. The upper panel shows simulated fMRI data generated using $E_{max} = 10.0$, $EC_{50} = \sqrt{2}$, $t_s = 0.50$, added to $1000 + .05t + 0t^2$ and Gaussian noise with SD$= 2$. In the lower panel, superimposed on the data is the predicted time course of drug effect over time, drawn using the parameter values returned by the Bayesian Data-Analysis Toolbox as most likely given these data and the PKPD model: $E_{max} = 10.6$, $EC_{50} = 1.43$, $t_s = 0.451$, $a_0 = 100\overline{0}$, $a_1 = 0.0553$, $a_2 = -0.000149$. For this time course, p(model) was estimated as 0.540, and the SD of the residuals was 2.04.

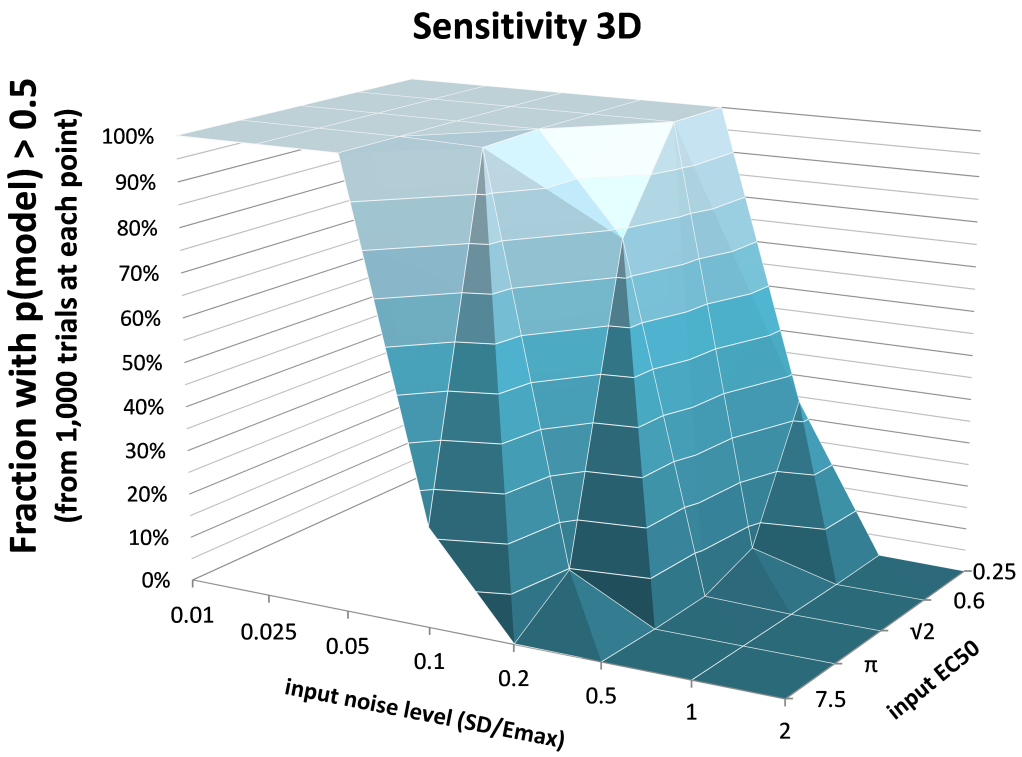

Figure 3. The fraction of time courses for which p(model) >0.5 is shown on the vertical axis as a function of the EC_{50} and SD used to generate the time courses.

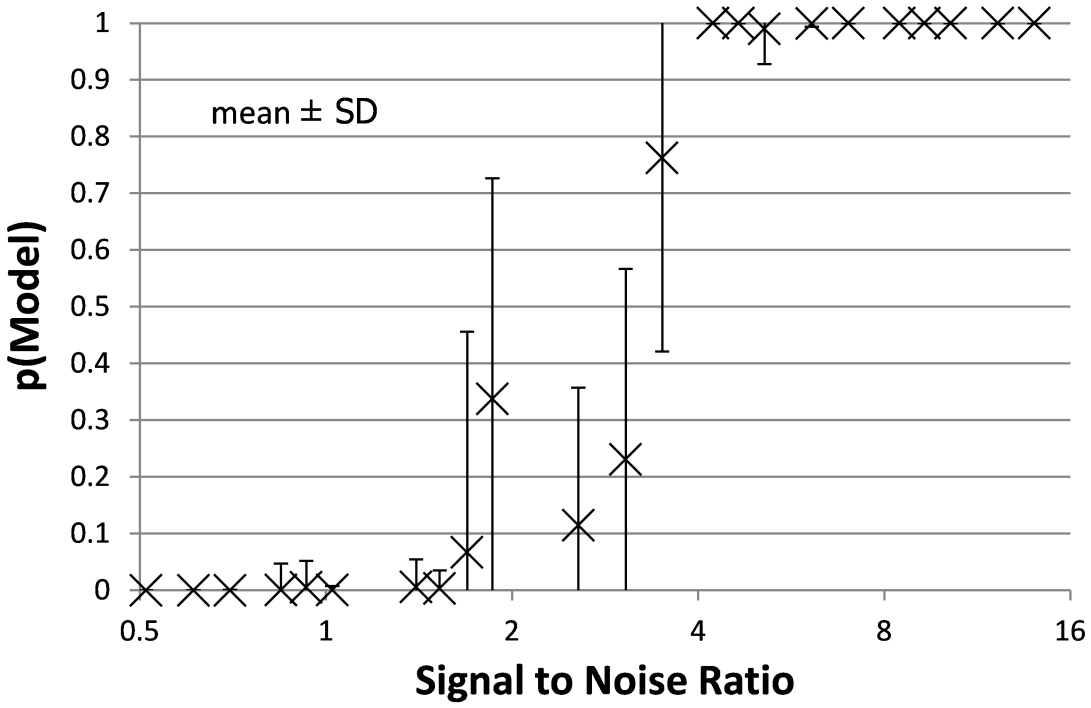

Figure 4. The mean ± SD probability of the full PKPD model is shown for each combination of EC_{50} and noise as a function of that combination's SNR as defined in Methods. Points with SNR outside the range shown here are omitted for clarity.

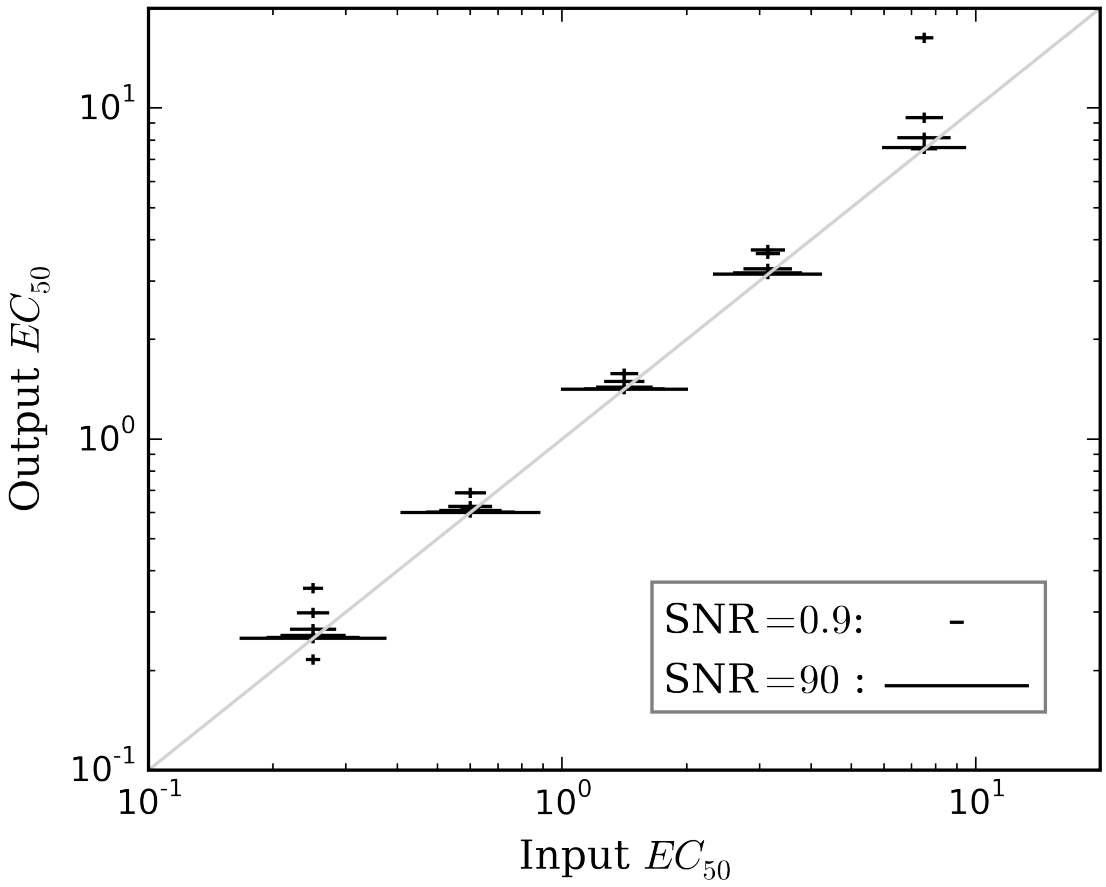

Figure 5. The mean accuracy of the estimated EC_{50} for time courses with $p(\text{model}) > 0.5$ is shown as a function of the input EC_{50}. SNR for each estimate is shown by the width of the marker, as indicated by the legend at lower right. The diagonal line indicates equality, *i.e.*, perfect accuracy.

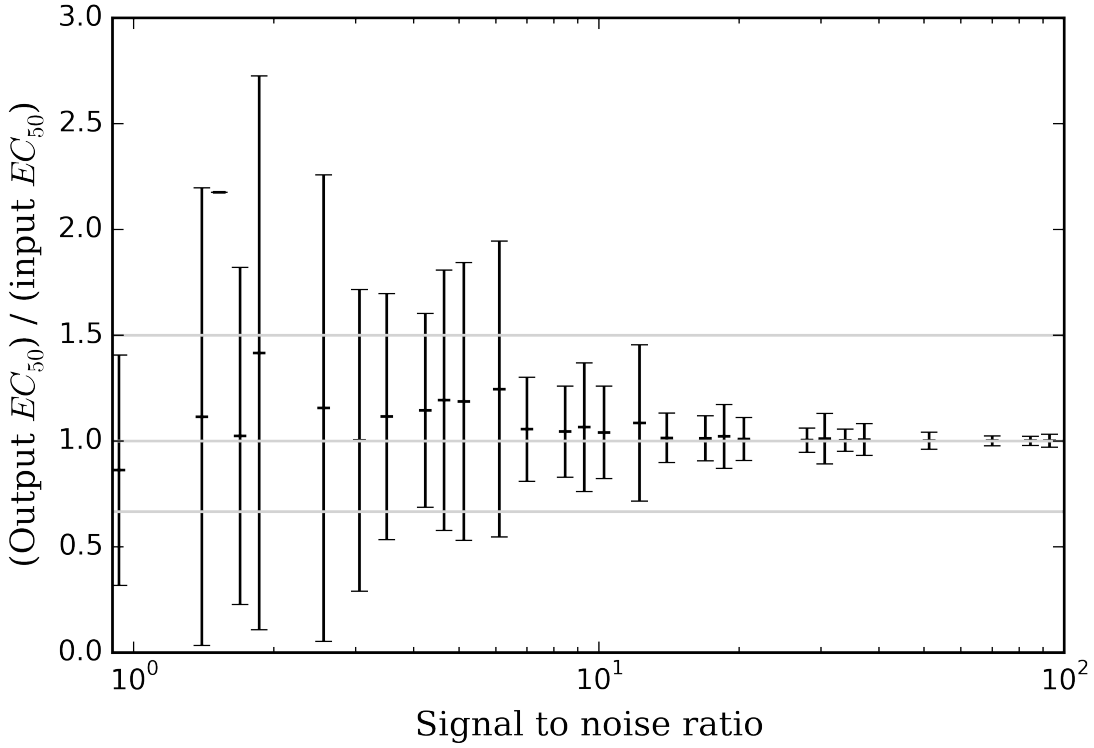

Figure 6. The mean ± SD accuracy of the estimated EC_{50} for time courses with p(model) >0.5 is shown as a function of SNR as defined in Methods. Here accuracy is defined as the output EC_{50} divided by the input EC_{50}. The full-width horizontal lines indicate perfect accuracy (ratio = 1.0) and 3/2 and 2/3 of perfect accuracy. The accuracy of the estimated EC_{50} is superb when SNR >about 6.5, and tends to be accurate for SNR as low as 0.9.

signal, until noise overwhelmed signal, *i.e.* when SNR $<$ about 3.5. The Bayesian Data-Analysis Toolbox successfully avoided false positives, correctly refraining from identifying a signal in every noise-only time course. In time courses with a signal, the errors are conservative, with EC_{50} usually erring on the high side (figure 6). Said differently, the most likely quantitative error is to report slightly lower sensitivity to drug, especially when sensitivity is in fact low.

The results from the simulated data suggest that this approach should be able to determine quantitative PD info from nonquantitative BOLD fMRI. We recently reported EC_{50} from a small phMRI (pharmacological fMRI) study analyzed using the "gold standard" approach, *i.e.* replicate measurements at each dose of drug, across a range of doses (Miller et al., 2013). The next step will be to apply the method validated here to similar phMRI data acquired in the same subjects specifically for QuanDyn^{TM} analysis, *i.e.* from experiments in which multiple doses were given within a single imaging session.

Limitations of the QuanDyn^{TM} quantitative pharmacodynamic imaging method include situations in which the PK/PD model, or the shape of the signal drift or noise used here, does not realistically model the data (discussed further in (Black et al., 2013)).

The QuanDyn^{TM} method described here has several potential advantages compared to the traditional approach to quantifying a drug effect, which is to estimate the population EC_{50} by sampling a wide range of doses, one dose per subject and several subjects per dose. That approach is an excellent choice when the population under study is homogeneous (*e.g.* an inbred rodent strain), but does not apply well to single subjects. One might adapt the traditional approach by repeatedly scanning a single subject, one dose per scan session, but that option brings its own complications, including scientific concerns such as sensitization or development of tolerance with repeated doses in addition to the practical and safety consequences of repeated scan sessions in each subject. That option, like the population method, would also require that subjects receive doses substantially higher than the EC_{50}, which may often be inappropriate in early human studies. Specifically, to estimate EC_{50}, traditional population PKPD studies require drug doses that produce effects of at least $\sim 95\% E_{max}$ (Dutta et al., 1996). For all these reasons, the QuanDyn^{TM} method may prove to be a better choice when single-subject responses are important, such as for medical diagnosis or individualized treatment dosing.

ACKNOWLEDGMENTS

Some of these results were presented previously (Koller JM, Bretthorst GL, Black KJ. A novel analysis method for pharmacodynamic imaging. Program #504.1, annual meeting, Society for Neuroscience, Chicago, 20 Oct 2009), and a preprint is being submitted simultaneously to bioRXiv.

COMPETING INTERESTS

Authors KJB and JMK have intellectual property rights in the QuanDyn^{TM} method (U.S. Patent #8,463,552 and patent pending 13/890,198, "Novel methods for medicinal dosage determination and diagnosis."). KJB is an Associate Editor for the Brain Imaging Methods section of Frontiers in Neuroscience.

AUTHOR CONTRIBUTIONS

Jonathan M. Koller performed the experiments, analyzed the data, contributed analysis tools, reviewed and critiqued the manuscript. M. Jonathan Vachon performed the experiments, analyzed the data, reviewed and critiqued the manuscript. G. Larry Bretthorst contributed analysis tools, reviewed and critiqued the manuscript. Kevin J. Black conceived and designed the experiments, performed the experiments, analyzed the data, wrote the paper.

DATA DEPOSITION

The following information was supplied regarding the deposition of related data:

The simulated data sets (1000 time courses for each set of parameter values and noise level) are available at the journal web site as Supplementary Data [total size $\sim$32MB].

FUNDING

Supported by the U.S. National Institutes of Health (NIH) grants R01 NS044598, 1 R21 MH081080-01A1 and 3 R21 MH081080-01A1S1, K24 MH087913 and R21 MH098670. NIH had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES

Black, K. J., Koller, J. M., and Miller, B. D. (2013). Rapid quantitative pharmacodynamic imaging by a novel method: Theory, simulation testing and proof of principle. *PeerJ*, 1:e117.

Bretthorst, G. L. (1988). *Bayesian Spectrum Analysis and Parameter Estimation*. Lecture Notes in Statistics. Springer-Verlag, New York.

Bretthorst, G. L. and Marutyan, K. (2014). Bayesian Data-Analysis Toolbox, v. 4.21 (software). Available at http://bayesiananalysis.wustl.edu (accessed 13 Feb 2015).

Dutta, S., Matsumoto, Y., and Ebling, W. F. (1996). Is it possible to estimate the parameters of the sigmoid E_{max} model with truncated data typical of clinical studies? *Journal of Pharmaceutical Sciences*, 85(2):232–239.

Miller, B., Marks, L. A., Koller, J. M., Newman, B. J., Bretthorst, G. L., and Black, K. J. (2013). Prolactin and fMRI response to SKF38393 in the baboon. *PeerJ*, 1:e195.