

Science Marches Forward

A New Tool to Study the Progress of Labor

FOR decades, carpenters used a mechanical level—a liquid-filled tube whose position is adjusted until a bubble is centered—to ensure the angles in their projects. In recent decades, mechanical levels have been supplanted by laser-driven devices. Now, an “app” permits an iPhone® (Apple, Inc., Cupertino, CA) to accomplish the same thing. So it is in science; new tools enable us to replace old tools and thereby enable us to ask new questions or old questions in a more precise manner. This issue of ANESTHESIOLOGY contains an article by Debiec *et al.*¹ describing this type of change.

The underlying causes of onset and progress of labor in humans remain a mystery and represent important public health concerns, given the high cost of premature birth. The wide interindividual variability of the progress of labor has always been of interest to obstetricians and anesthesiologists. Anesthesiologists have been primarily concerned over the past two decades with whether their interventions, such as epidural analgesia, slow the progress of labor. The tool used most often to examine the progress of labor is based on work done by an obstetrician, Friedman,² initially in the 1950s. Friedman tracked the course of labor (quantified by cervical dilatation) in 500 primigravid parturients and then quantified the time course of labor (cervical dilatation *vs.* time). His model consisted of two portions: a shallow linear phase (“latent” labor) and a steeper curvilinear portion (“active” labor). The active portion was further divided into four portions: an acceleration phase (the transition between latent and active labor), a linear portion (“phase of maximal slope”), a curvilinear portion (“deceleration phase”), then a plateau at full dilatation (“second stage”).

Friedman’s approach offered limited opportunity for mathematical analysis. Thus, the richness of data collected over the course of labor underwent minimal scrutiny. Perhaps important issues could not be addressed because the analysis tools were lacking. De-

biec *et al.*¹ applied methods commonly associated with pharmacokinetic analysis to labor data. To accomplish this, they first needed to define a “model,” *i.e.*, to assess the “shape” of the time course of labor. Whereas Friedman had described the course of labor with intersecting lines, Debiec *et al.*¹ concluded that a continuous function based on exponentials worked better in their hands. They then needed to determine if a single exponential or the sum of two exponentials was justified by the data. This is similar to the process in pharmacokinetic analyses, where one decides between one- and two-compartment models. Having found a model that fit the data, the authors could then evaluate the effects of covariates (*e.g.*, did the course of labor differ as a function of self-proclaimed race?). Although the results of this manuscript focus on the latter, the major contribution of Debiec *et al.*¹ is actually development of the model.

The method used by Debiec *et al.*¹ is called “mixed-effects modeling” in which the relative contribution of fixed-effects (things that one can measure; in this case, things like ethnicity) and random effects (random variability among subjects that cannot be attributed to measurable characteristics) are considered. In medicine, the first major use of mixed-effects modeling was for pharmacokinetic analysis. In particular, the computer program NONMEM (*non-linear mixed effects modeling*) was developed at the University of California, San Francisco, by the late Lewis Sheiner, M.D., Ph.D. (Professor, Departments of Laboratory Medicine and Biopharmaceutical Sciences, University of California San Francisco, California, 1940–2004) and Stuart Beal, Ph.D. (Professor of Laboratory Medicine, University of California, San Francisco, 1941–2006) to facilitate modeling of drug behavior. Much seminal work in anesthesia has been performed by using NONMEM, and it is rare for an issue of a major anesthesia journal to appear without one or more articles that depend on its use. However, the article by Debiec *et al.*¹ probably represents the first application of mixed-effects modeling to the time course of labor.

By using NONMEM, the authors identified the effects of several maternal characteristics that influence the time course of labor with high degrees of statistical significance. Debiec *et al.*¹ also showed that the magnitude of these effects was trivial, despite their statistical significance. From their analysis, we learn that the factors measured in their study do not explain why some women have fast labor and others have slow labor. However, the authors have provided a sharp

This Editorial View accompanies the following article: Debiec J, Conell-Price J, Evansmith J, Shafer SL, Flood P: Mathematical modeling of the pain and progress of the first stage of nulliparous labor. ANESTHESIOLOGY 2009; 111:1093–110.

Accepted for publication July 22, 2009. The software (PLT Tools) used by Debiec *et al.* was developed and is owned jointly by Dr. Fisher and Steven Shafer, M.D. (senior author of the Debiec *et al.* article).

Timothy J. Brennan, Ph.D., M.D., served as Handling Editor for this article; James C. Eisenach, M.D., was not involved in the decision-making process.

tool to quantitatively assess the effect of any patient or environmental covariate (*e.g.*, genetic influences, barometric pressure) on the time course of labor. Understanding the causes of interindividual variability in physiologic responses, disease progression, and response to therapy is a central theme to 21st century biomedical research. Debiec *et al.*¹ have provided an important tool to perinatal and pain medicine to probe root causes of such variability in progress of labor and the pain it causes.

Dennis M. Fisher, M.D.,* James C. Eisenach, M.D.† *P Less Than Company, San Francisco, California. fisher@PlessThan.com. †Department of Anesthesiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

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■ ANESTHESIOLOGY REFLECTIONS

The Horton Intercoupler



Surgeon-manufacturer Karl Connell (1878–1941) was alarmed by the fatal explosion in Boston resulting from static ignition of cyclopropane vapor delivered by one of his Connell DeLuxe anesthesia machines. He collaborated in 1939 with a Massachusetts Institute of Technology professor of engineering, J. Warren Horton, and a Lahey Clinic anesthesiologist, Phillip D. Woodbridge, to produce the “Horton Intercoupler” (*see above*). This device used its metal casing, woven metallic bracelets, spring clamps, and often a drag chain to provide high-resistance electric coupling of the patient, the anesthesiologist, the operating room table, and the anesthesia machine to the conductive flooring. Once nonexplosive gases were introduced as general anesthetics, use of the cumbersome Horton Intercoupler waned. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Mathematical Modeling of the Pain and Progress of the First Stage of Nulliparous Labor

Jozef Debiec, M.D.,* Jessamyn Conell-Price, B.A.,† Jennifer Evansmith,‡ Steven L. Shafer, M.D.,§ Pamela Flood, M.D.||

Background: Patient characteristics may contribute to the progress and pain of labor. Quantitative evaluation of the effects of patient characteristics requires robust mathematical models of labor progress and labor pain.

Methods: The authors retrospectively studied 100 sequential deliveries from each of five self-reported ethnic groups (Asian, Black, Hispanic, Other, and White). Demographic variables, cervical dilation, and numerical rating scores for pain before analgesia and cervical dilation were abstracted from the automated medical record. Labor progress was modeled with a biexponential function describing the latent and active phases of labor. Labor pain was modeled as a sigmoid function of cervical dilation by using a previously validated mathematical model. The covariates, including self-described ethnicity, were analyzed with NONMEM.

Results: The biexponential function described the time course of labor progress better than several alternative functions, including the sigmoidal function introduced by Friedman. The sigmoidal function of labor pain described its dynamic nature well, with substantial intersubject variability. Asian women had slower active labor than other ethnicities ($P < 0.01$). Asian women also reported less pain during their labor compared to all other patients ($P < 0.001$). Slower labor progress was associated with less rapid progression of pain, but this did not obviate the effect of Asian ethnicity on pain. Neuraxial analgesia is strongly associated with slower labor ($P < 0.0001$). Greater maternal weight was associated with slower active labor ($P < 0.0001$).

Conclusions: Mathematical models can be used to detect subtle effects of patient covariates on the progress and pain of the first

stage of labor. Asian women and heavier women had slower labor and slower onset of labor pain than others. These effects were modest compared with the substantial remaining unexplained subject-to-subject variability in labor progress and labor pain.

PAIN increases over the course of labor and is highly variable among individuals.¹ Although many physical and physiologic factors have been linked to the amount of labor pain women experience,² it is difficult to discern the contribution of individual factors because the pain intensity changes with cervical dilation.¹ As such, a model of labor progress is required to assess the effects of patient demographics and medical interventions on labor pain.

Several genetic polymorphisms that affect pain sensitivity have been described.^{3,4} Recently, studies have shown that ethnic differences exist in the duration of the second stage of labor and in the likelihood of Cesarean delivery.^{5,6} Even though the use of ethnicity as a marker of genetic variation has been debated,⁷ we hypothesized that a patient's self-identified ethnicity might predict labor pain and progress.

In a retrospective cohort trial of 500 nulliparous parturients, we looked for associations among self reported ethnicity (Asian, Black, Hispanic, White, or Other), labor progress, and labor pain. We also investigated the influence of weight, height, maternal age, gestational age, and birth weight, neuraxial analgesia, oxytocin administration, labor induction, or rupture of membranes on labor progress and pain. We used mixed effects models to describe pain and progress of labor, and we tested the effects of these covariates on our models. This required development of a novel model for labor progress, and then we used this model to predict cervical dilation in our model of labor pain.

Materials and Methods

This retrospective cohort study was approved by the Institutional Review Board of Columbia University Medical Center (Columbia University Review Board, New York, NY). The requirement for informed consent was waived. Five hundred eligible parturients were identified by screening delivery records at the Columbia University-affiliated Sloane Hospital for Women. Working backward from May 2008, we gathered the data for this study from the first one hundred eligible women from each ethnic group. The inclusion criteria were (1) healthy nulliparous parturients aged 18–45 yr, (2) gestational age of 37–42 weeks, and (3) vaginal delivery of a singleton infant with birth weight 2.5–4.0 kg. Patients with preeclampsia and chronic pain syndromes were excluded.

◆ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Fisher DM, Eisenach JC: Science marches forward: A new tool to study the progress of labor. ANESTHESIOLOGY 2009; 111:936-7.

🌐 Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

* Post Graduate Residency Fellow, † Research Coordinator, § Professor of Anesthesiology, || Associate Professor of Clinical Anesthesiology, Department of Anesthesiology, Columbia University; ‡ Undergraduate Student, Columbia College, Columbia University.

Received from the Department of Anesthesia, Columbia University, New York, New York. Submitted for publication September 18, 2008. Accepted for publication July 8, 2009. Support was provided solely from institutional and/or departmental sources. Dr. Shafer is co-developer of PLT Tools and has a financial interest in the software. Dr. Flood is married to Dr. Shafer. Presented at the annual meeting of the American Society of Anesthesiologists, Orlando, Florida, October 19, 2008.

Address correspondence to Dr. Flood: Department of Anesthesiology, Columbia University, New York, New York 10032. Pdf3@columbia.edu. This article is available for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Labor was managed by residents supervised by an attending obstetrician who was in the hospital. Patients were managed by using a standard clinical protocol with cervical examination every 4 h during latent labor and every 2 h during active labor unless otherwise clinically indicated. We gathered the numerical rating scale for pain, cervical dilation measurements, labor interventions, and time of observations for this study from the electronic medical record. Cervical dilation measurements were reported in 1 cm increments from 0 cm (closed cervix) to 10 cm (fully dilated cervix). Numerical rating scale (NRS) scores with contractions were recorded by obstetrical nurses and physicians by using an 11-point scale (0 for no pain and 10 for the worst pain imaginable). Patients were instructed to rate their pain at the peak of a contraction. Pain scores were requested on admission, with evidence of significant change in status and after treatment. Pain scores reported after patients received any analgesia are not considered in the model. Most labor nurses are bilingual in English and Spanish. When the patient could not converse in either language, a standard translation protocol was initiated as required by law.

We extracted labor characteristics (*e.g.*, when membranes were ruptured) and labor interventions (*e.g.*, when labor was induced, when oxytocin was administered, when analgesia was initiated) from the electronic medical record. We also obtained maternal weight, maternal height, maternal age, gestational age, and birth weight that were recorded from a structured nursing interview from the electronic medical record. Self-reported ethnicity was recorded by labor and delivery administrative personnel according to categories derived from the 2000 census. Although people of Hispanic ethnicity can be of any race, patients are asked to choose only one category.

Statistics and Data Analysis

Demographic and labor characteristics were compared among self-identified ethnic groups. Continuous variables were assessed for normality by using the Kolmogorov-Smirnov test. Normally distributed data are reported as mean \pm SD and analyzed by using ANOVA. Nonnormally distributed data are reported as median (range). Differences among nonnormally distributed data are compared with a Mann-Whitney test for two group comparisons or a Kruskal-Wallis test for three or more groups (GraphPad InStat 3.06, San Diego, CA). For categorical data, relative risk was calculated by comparing each ethnic group's characteristic to the population characteristic using chi-square analysis (GraphPad InStat 3.06). $P < 0.05$ was considered significant. The labor progress and labor pain models were analyzed with NONMEM (Nonlinear Mixed-Effects Modeling; Globomax, Ellicott City, MD) using PLT Tools (PLT Soft, San Francisco, CA). One hundred parturients were enrolled in

each group; in our previous study with 100 subjects in test and training sets, we were able to identify a covariate effect with the magnitude of 1 NRS point.¹ We consider this difference to be minimally clinically significant.

Labor Progress Model

We used a population approach to model the progress of labor. The labor progress model was then used in the model of labor pain. The development of the labor progress model is described in detail in the appendix. To briefly summarize, the times of each cervical exam were converted to the number of hours before the first measurement of full dilation (10 cm), which was considered time = 0. This was necessary because data collection did not begin at the same time in each patient, and cervical dilation was assessed more frequently as it progressed towards complete dilation. Thus, the first recording of full cervical dilation was chosen as the time-point to align the individual labor progress curves. In our analysis, time is reversed from usual clock time and proceeds along the x-axis from 0 (the time of complete cervical dilation) and is the number of hours before complete cervical dilation. Treating active and latent labor as linear, as originally described by Friedman,⁸ produced fits that were extraordinarily dependent on initial parameter estimates and not suitable for hypothesis testing. We tested linear, sigmoidal, and single exponential functions that were significantly inferior to a biexponential model (see appendix).

We therefore chose a biexponential model, $Dilation = Ce^{-\lambda_1 t} + (10-C)e^{-\lambda_2 t}$, where λ_1 and λ_2 are rate constants of active and latent labor, respectively, and where C is the number of centimeters of dilation associated with the active phase of labor. τ is time. This model produces similar predictions to the bilinear model, but it is suitable for hypothesis testing with NONMEM. We used an exponential model for interindividual variability and an additive model for intraindividual variability. The full data set is provided as an Excel file (see Supplemental Digital Content 1, <http://links.lww.com/ALN/A556>), and the NONMEM control files (see Supplemental Digital Content 2, <http://links.lww.com/ALN/A557>, which is the NONMEM control file for the final labor progress model, and Supplemental Digital Content 3, <http://links.lww.com/ALN/A558>, which is the NONMEM control file for the final labor pain model) are available as text files.

We modeled the effect of time invariant continuous covariates, including age, weight, height, gestational age, and birth weight, as a proportional change in the values of λ_1 , λ_2 , or C. For example, $\lambda_1 = \theta_1 + \theta_2 \times (\text{patient age} - \text{median age})$, where θ_1 is the nominal value of the parameter and θ_2 is effect of age on the parameter. We modeled the effect of ethnicity by introducing new parameters into the model for each ethnic group. We modeled the effect of abrupt changes in patient state during labor

(initiation of neuraxial analgesia, rupture of membranes, initiation of an oxytocin infusion) by using a time scale factor, as described in the appendix.

In each case, models were assessed for statistical significance by using the improvement in the objective function (-2 Log Likelihood - equivalent to the sum of squares in linear regression) with the likelihood ratio test. An improvement in -2 Log Likelihood greater than 6.63 with the introduction of a new parameter was considered statistically significant (chi-square distribution for $P < 0.01$ with 1 degree of freedom). The model parameters were estimated by NONMEM using the "first order conditional estimation" approach. We chose $P < 0.01$ rather than $P < 0.05$ in building the models to compensate (in part) for the large number of models examined in the process of model development.

We first explored whether treatment factors (initiation of neuraxial analgesia, oxytocin administration, induction of labor, or rupture of membranes) influenced the nominal progress of labor. Once these factors were incorporated into a model of labor progress, we explored the influence of the time invariant patient covariates weight, height, maternal age, gestational age, and birth weight. The completed model was then used to see if self-identified ethnicity further informed the progress of labor model. This order of analysis was chosen so that only an influence (if any) of self-identified ethnicity other than differences in weight, height, maternal age, gestational age, or birth weight would be captured.

Confidence in each parameter was assessed by using log likelihood profiling and bootstrap analysis. The log-likelihood profile calculated the -2 log likelihood by fixing the value of the parameter at different estimates and reestimating the other model parameters. Parameters that are known with certainty are expected to have a narrow range before the -2 log likelihood increases by more than 3.84 (chi-square distribution for $P < 0.05$, 1 degree of freedom). The bootstrap was calculated by randomly sampling a new data set from the patient data, with replacement, and then repeating the NONMEM analysis. This procedure was repeated 1,000 times. A 95% confidence interval was calculated from the bootstrap analysis as the interval from the parameter value at the 2.5% rank to the parameter value at the 97.5% rank. The log likelihood profile addresses the confidence in the parameter relative to the overall model. The bootstrap analysis addresses the confidence in the parameter relative to the data.

The improvement introduced from analysis of covariates was assessed by using a jackknife crossvalidation procedure in which the data were randomly grouped into 10 subsets. In 10 separate analyses, 9 of the 10 subsets were grouped, and the model was estimated from those data. The model was then applied to the excluded subset, and the median weighted residual error and the median absolute

weighted residual error were calculated for the excluded subset. The median weighted residual was calculated as $\text{median}\left(\frac{\text{measured dilation} - \text{predicted dilation}}{\text{predicted dilation}}\right)$. The median absolute weighted residual was calculated as $\text{median}\left(\left|\frac{\text{measured dilation} - \text{predicted dilation}}{\text{predicted dilation}}\right|\right)$. This was repeated 10 times, each time excluding one-tenth of the data.

Labor Pain Model

We used the labor pain model that we have previously reported.¹ The NRS pain response to cervical dilation was fit to a sigmoid equation:

$$\text{NRS} = \text{NRS}_{\text{MIN}} + (\text{NRS}_{\text{MAX}} - \text{NRS}_{\text{MIN}}) \frac{\text{CD}^{\gamma}}{\text{CD}^{\gamma} + \text{CD}_{50}^{\gamma}}$$

with four parameters by using NONMEM. CD is the cervical dilation predicted by the labor progress model, NRS_{MIN} is the minimum reported pain score, NRS_{MAX} is the maximal reported pain score, CD_{50} is the cervical dilation associated with 50% of maximal pain, and γ is the steepness of the sigmoidal relationship. This model assumes that for a population of laboring women, reported pain with contractions is modest when the cervix is closed and increases in intensity as the cervix dilates, reaching maximum intensity when the cervix is fully dilated. The assumption of monotonicity was verified by tallying the number of women who reported a decrease in pain during labor and by qualitatively assessing the distribution of bias and the fit of the model to the raw data.

For two reasons, we modeled pain as a function of the *post hoc* individual Bayesian predicted cervical dilation from the labor progress model, rather than the actual measured dilation. First, some pain measurements did not have associated cervical dilations. Using the individual *post hoc* Bayesian predicted dilations provided a predicted cervical dilation at every point in time. Second, the *post hoc* Bayesian predicted dilation is arguably a more accurate measurement than an actual measurement, both because the actual measurement is always reported as an integer and because the prediction represents, in part, an average of many predictions. Consider progressive cervical examinations of 4, 4, 5, and 5. A more accurate estimate of the "true" cervical dilation might be 4.0, 4.5, 5.0, and 5.5 cm, which is what the *post hoc* Bayesian prediction would reflect.

We tested whether the sigmoidal model was better than a simple linear model. We then fit the sigmoidal model of NRS as a function of predicted cervical dilation, and we systemically evaluated the effects of weight, height, maternal age, gestational age, and birth weight on each parameter of the model. We then tested whether the presence or absence of an oxytocin infusion, labor

induction, and rupture of membranes affected the parameters of the model. We did not test neuraxial analgesia; by definition, all data following the initiation of neuraxial analgesia initiation were censored from the analysis. Lastly, we tested the effect of the instantaneous *rate* of dilation on each of the model parameters.

Once the model incorporated the effects (if any), of weight, height, maternal age, gestational age, birth weight, oxytocin administration, labor induction, rupture of membranes, and the instantaneous rate of dilation we tested whether self-identified ethnicity affected any of the parameters. As described for the labor progress model, we took this approach to identify only an effect of ethnicity (if any) not already explained by other patient covariates. In addition, we tested each possible combination of ethnicities to identify the most parsimonious model that properly accounted the effect (if any) of self-reported ethnicity on time course of labor pain. The calculation of instantaneous rate is shown in the appendix.

We used additive models for interindividual variability in NRS_{MIN} and NRS_{MAX} , and we used an exponential model for the interindividual variability in CD_{50} . Because interindividual variability was miniscule on NRS_{MAX} , it was fixed in our final model. No interindividual variability was modeled for γ . We used an additive model of intraindividual residual error. Control files for the final model is provided as Supplemental Digital Content 3, <http://links.lww.com/ALN/A558>.

Confidence in each parameter in the labor pain model was assessed as described for the labor progress model. However, the log likelihood profiles produced curves with fluctuations as a result of the very steep value of γ in the model, causing a near step-function around CD_{50} . This hindered NONMEM from accurately searching the parameter space. After verifying that the steepness of the relationship around CD_{50} had not precluded NONMEM from converging on the optimal model, log likelihood profiles were run approximately 100 times with different starting parameters and occasionally with some parameters of the model fixed to verify that the curves were unimodal and to force NONMEM to further explore the parameter space. Lastly, for several log likelihood profiles, some residual jaggedness was removed by manually selecting local minimum values.

Results

Delivery records from October 2006 to May 2008 were screened (6,524 women). Enrollment and exclusion criteria are shown in figure 1. The five self-reported groups that have major representation in our population are Asian (12%), Black (12%), Hispanic (30%), White (29%), and Other (18%). All Hispanic and White women were delivered between May 2007 and May 2008. Because of their decreased frequency, Black, Asian, and Other

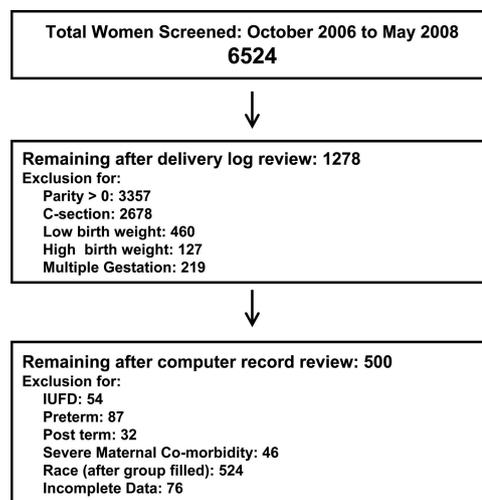


Fig. 1. Screening, exclusion, and enrollment. Flow sheet for subjects screened from October 2006 to May 2008 with specific exclusion criteria. Some patients were excluded for more than one indication. IUFD = intrauterine fetal demise.

women were delivered between October 2006 and May 2008. The demographic characteristics of these five groups are shown in table 1. Gestational age, maternal age, height, weight, birth weight, and emotional status did not differ among the five groups. Employment, marital status, and primary language varied among groups. On the basis of an analysis of primary and secondary languages, the Other group consists of a large number of subjects with mixed ethnicity, and the Asian group is composed of patients from many countries in Asia including China, Japan, Korea, India, and the Philippines.

The characteristics of labor and its management are described in table 2. Overall, 27% of patients were admitted for induction of labor, 60% of patients received oxytocin during the first stage of labor, and 94% of patients received labor analgesia. The majority of patients were treated with combined spinal epidural analgesia or epidural analgesia, treatments which are referred to collectively as neuraxial anesthesia. Three percent of patients were treated with opioids for labor analgesia. Induction, oxytocin, and analgesia rates were similar among groups. The cervical exams at arrival to the hospital are also similar among the groups. The length of the second stage of labor was significantly shorter for Black women (median 1.1 h) and longer for the Other group (median 1.7 h) compared with the overall population, who had a median second stage of labor of 1.4 h. Hispanic women were more likely than others to have their membranes artificially ruptured than other women (relative risk = 1.4).

Labor Progress Model

As explained in the appendix, the biexponential model accurately captured the shape of the progress of labor. Maternal age, height, gestational age, birth weight, oxytocin infusion, labor induction, and rupture of mem-

Table 1. Demographic Characteristics of 500 Nulliparous Women

	Overall (n = 500)	Asian (n = 100)	Black (n = 100)	Hispanic (n = 100)	Other (n = 100)	White (n = 100)
Gestational age, weeks	39 ± 1	39 ± 1	39 ± 1	39 ± 1	39 ± 1	39 ± 1
Median age, yr	29 (18–44)	30 (19–41)	27 (18–39)	26 (18–42)	30 (18–44)	31 (19–41)
Weight, kg	78 ± 15	74 ± 13	84 ± 20	76 ± 12	74 ± 11	81 ± 16
Height, cm	163 ± 9	162 ± 7	164 ± 6	164 ± 14	163 ± 6	161 ± 9
Baby weight, kg	3.23 ± 0.37	3.17 ± 0.36	3.15 ± 0.35	3.24 ± 0.36	3.31 ± 0.40	3.28 ± 0.38
Employment, % employed*	52	65	46	31	54	65
Marital status, % married*	66	93	40	39	67	93
Emotional status, % happy	82	81	82	80	85	84
Primary language, % English*	71	70	76	40	75	91

Normally distributed data are shown as mean ± standard deviation; otherwise median and range are shown. Relative risk (RR) compares the value for the specific group to the population characteristic. Gestational age, maternal age, weight, height, baby weight, and emotional status did not differ among groups. Hispanic mothers were more likely to be unemployed: RR 1.7 (1.2–2.4). Asian and White mothers were less likely to be single: RR 0.71 (0.61–0.83) for both groups. Black and Hispanic mothers were more likely to be single: RR 1.7 (1.2–2.2) for Blacks and 1.7 (1.3–2.2) for Hispanics. English was more likely to be a second language for Hispanic women and less likely for White women: RR 1.8 (1.4–2.3) and RR 0.78 (0.68–0.9), respectively.

* $P < 0.001$.

branes did not significantly affect the progress of labor. As shown in table 3, self-identified Asian ethnicity, increasing maternal weight, and presence of neuraxial analgesia were associated with significantly slower labor. The model was built by first incorporating the strongest effect (presence of neuraxial analgesia) and then incorporating the next strongest effect (weight) and finally adding the effect of self-identified ethnicity. Thus, the P values shown in table 3 represent the P values for the incremental improvement, and they are thus conservative relative to the improvement that might be observed from assessment of the covariate effect in the absence of other explanatory covariates.

Figure 2 shows all of the labor progress data for (A) an initial model without covariates and (B) the final model with the covariate effects. The top figures show the observations as vertical lines and the individual *post hoc* predictions (gray lines). Figures 2C and 2D show the error in the fits, based on the population values of the parameters (e.g., with interindividual variability set to 0). The fit for the initial and final models are almost visually indistinguishable. Indeed, the median absolute predic-

tion error for the initial model is 0.98 cm, which the model incorporating covariates has only improved to 0.94 cm. Figure 3 shows the predicted (X axis) *versus* measured (Y axis) cervical dilation for (A) the initial model and (B) final covariate adjusted model. As noted for figure 2, the improvement in fit with the inclusion of covariates is almost invisible in the figure. Thus, even though the covariate effects shown in table 3 are highly statistically significant, they represent very small improvements in the model.

Figure 4 shows the log-likelihood profiles and 95% confidence intervals for active labor rate constant (λ_1), latent labor rate constant (λ_2), and the coefficient (C) on the model parameters in the Non-Asian and Asian patients. Figure 5 shows log-likelihood profiles and 95% confidence intervals for the neuraxial analgesia scale factor and the effect of weight on the active and latent rate constants. In every case, the parameter estimates are well constrained within the boundaries of the model and do not cross 0, showing that they are statistically different from 0. The likelihood profiles similarly reach the edges of the 95% confidence interval derived from the

Table 2. Labor Characteristics for 500 Nulliparous Women

	Overall (n = 500)	Asian (n = 100)	Black (n = 100)	Hispanic (n = 100)	Other (n = 100)	White (n = 100)
Cervical exams/patient*	5 (1–15)	5 (1–12)	6 (1–15)	5 (1–13)	4 (1–14)	5 (1–13)
Labor induction, %	27	28	33	21	30	23
Spontaneous rupture of membranes, SROM %†	49	55	62	34	45	45
NRS observations/patient*	1 (0–10)	1 (0–3)	1 (0–3)	1 (0–5)	1 (0–4)	1 (0–10)
Analgesia, %	94	91	95	91	97	96
Second stage, h*	1.4 (0.1–1.8)	1.8 (0.0–8.8)	1.1 (0.1–6.7)	1.3 (0.1–4.8)	1.9 (0.0–10.8)	1.6 (0.0–5.3)

The number of cervical exams per patient varied significantly by race ($P < 0.001$, Kruskal-Wallis test). Values are medians (range). Relative risk (RR) compares the value for the specific group to the population characteristic. Blacks and Hispanics had more exams than Others ($P < 0.01$, 0.05). There was no difference in the incidence of labor induction. Hispanics have higher RR of AROM 1.4 (artificial rupture of membranes, 1.0–2.0; Fisher Exact test). The number of numerical rating scale (NRS) per patient varied significantly by ethnicity ($P < 0.001$, Kruskal-Wallis test). Asians had lower scores than Hispanics and Whites ($P < 0.001$). There was no difference in the percentage of patients who had analgesia during the first stage of labor. The second stage of labor was shorter in Blacks than Asians, Others, and Whites (0.01, 0.05).

* $P < 0.001$; † $P < 0.05$.

SROM = spontaneous rupture of membranes.

Table 3. Labor Progress Model

Parameter	Parameter	Approximate CV*	P Value	95% Confidence Interval
Non-Asians				
Active labor rate constant, hr ⁻¹	0.65			0.51 to 0.85
Latent labor rate constant, hr ⁻¹	0.11			0.10 to 0.13
Coefficient, cm	4.6			4.0 to 5.2
Asians				
Active labor rate constant, hr ⁻¹	0.48	88%	0.009	0.34 to 0.73
Latent labor rate constant, hr ⁻¹	0.07	48%	0.009	0.05 to 0.09
Coefficient, cm	5.8	19%	0.009	4.8 to 6.6
Epidural scale factor	0.63		< 0.0001	0.48 to 0.78
Weight factors				
On active labor rate constant, kg ⁻¹	0.0084		< 0.0001	0.0012 to 0.0167
On latent labor rate constant, kg ⁻¹	-0.011		< 0.0001	-0.016 to -0.006
Errors				
Median error, cm	0.19			
Median absolute error, cm	0.94			

* The approximate coefficient of variance (CV) is actually the standard deviation of the interindividual variability in the log domain.

bootstrap analysis at roughly the $P < 0.01$ range. This shows that the likelihood profiles are not dependent on particular patients or observations.

Figure 6A shows predictions of the labor progression model moving forward in time from 1 cm of cervical dilation. The “nominal” patient is a non-Asian patient of median weight without neuraxial analgesia. The prediction for that patient appears as a black line. Representative predictions are shown for an Asian patient (red line) also of median weight without neuraxial analgesia, a non-Asian patient of the lightest weight in the population (48 kg, blue line), a non-Asian patient of the heaviest weight in the population (171 kg, green line), a nominal patient with neuraxial analgesia placed at 1 cm of cervical dilation (dashed line) and 4 cm of cervical dilation

(dotted line). The effect of neuraxial analgesia is visible as a very slight slowing in rate. Figure 6B is the prediction as determined by the model.

Figure 7A shows the individual *post hoc* Bayesian fits for the model used to interpolate cervical dilations. The only covariate incorporated in this model is the presence of neuraxial analgesia. As explained in the methods, labor pain was modeled as a function of the cervical dilation predicted by the labor progress model. This provided a predicted cervical dilation at every timepoint. The model was based on incorporation of the neuraxial analgesia effect, which is associated with a different progress of labor. The median error was 0.01 cm and the median absolute error was 0.42 cm. Figure 7B shows the final *post hoc* Bayesian

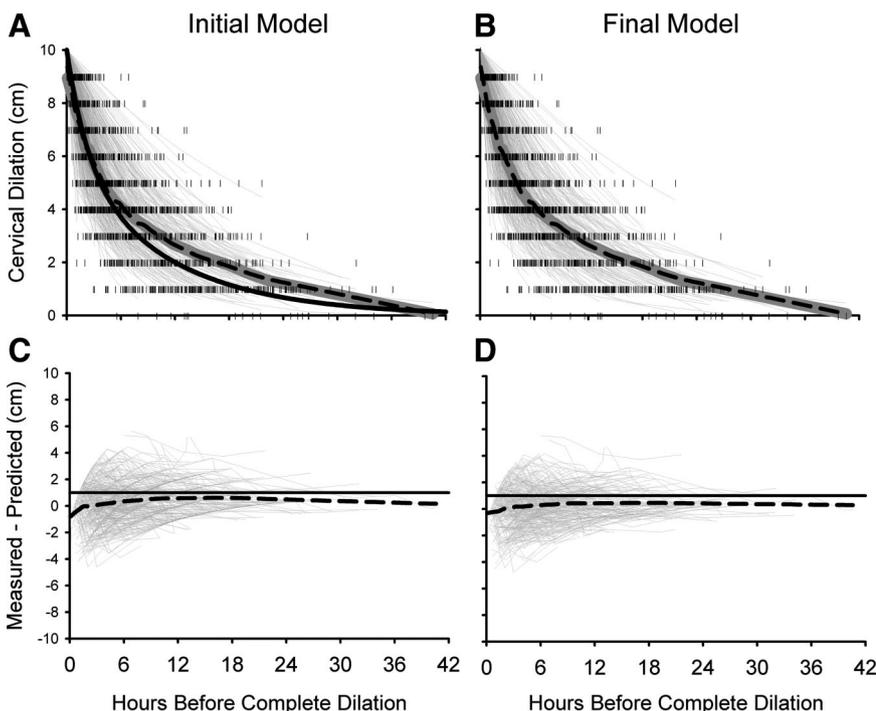
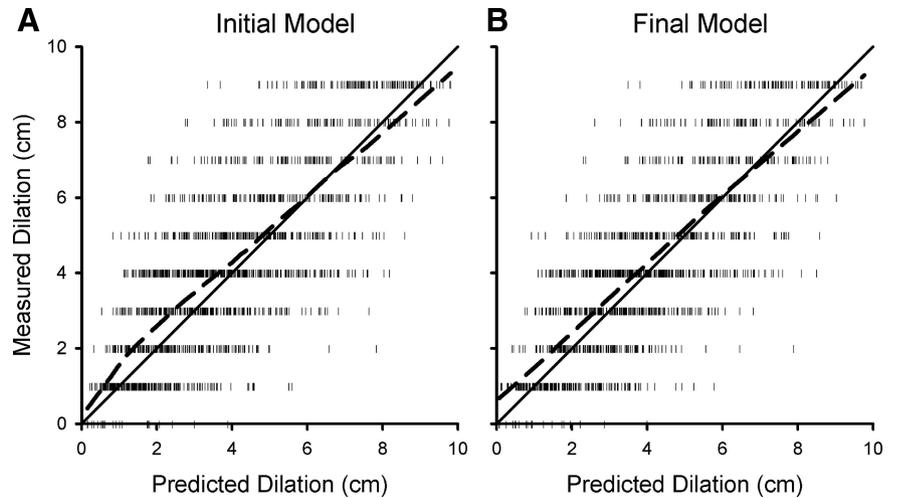


Fig. 2. Labor progress data. *Small vertical lines* are data points, and *gray lines* are individual fits. (A) Initial model without covariates, *solid black line* represents the typical individual, *thick gray line* represents a supersmoother through the data, and the *dashed line* is a supersmoother through the *post hoc* estimates. (B) Final model incorporating covariate effects, *thick gray line* represents a supersmoother through the data, and the *dashed line* is a supersmoother through the *post hoc* estimates. (C and D) Individual measured-predicted observations over time for the initial and final models are *thin gray lines*. The *dashed line* is a supersmoother through the data. Asian ethnicity, presence of neuraxial analgesia, and maternal weight were included as covariates in the final model. All data points are represented in the initial model. The final model excludes patients in whom weight was not recorded ($n = 98$ excluded).

Fig. 3. Predicted (X axis) versus measured (Y axis) cervical dilation. (A) Initial model and (B) final covariate adjusted model. The dashed lines are super-smoothers through the data. Asian ethnicity, presence of neuraxial analgesia, and maternal weight were included as covariates in the final model.



estimate for the final covariate model. It is almost indistinguishable visually from the top graph. This model was not used for the labor pain analysis because it excludes those patients whose weights were not recorded. The bias and accuracy is similar to the upper figure, with a median error of +0.005 cm and a median absolute error of 0.43 cm.

The magnitude of unaccounted for intersubject variability can be estimated by comparing the residual error for the population model (fig. 2D, median error = 0.94 cm) with the residual error in the individual *post hoc* Bayesian model (fig. 7B, median

error = 0.43 cm). There is considerable intersubject variability that is not accounted for by the covariates assessed in this study.

Labor Pain Model

Maternal weight, height, maternal age, gestational age, birth weight, oxytocin infusion, labor induction, and rupture of membranes did not significantly affect the relationship between cervical dilation and NRS score. As shown in table 4, self-identified Asian ethnicity and the instantaneous rate of labor affected the relationship of cervical dilation to NRS score. Thus, *P* values shown in

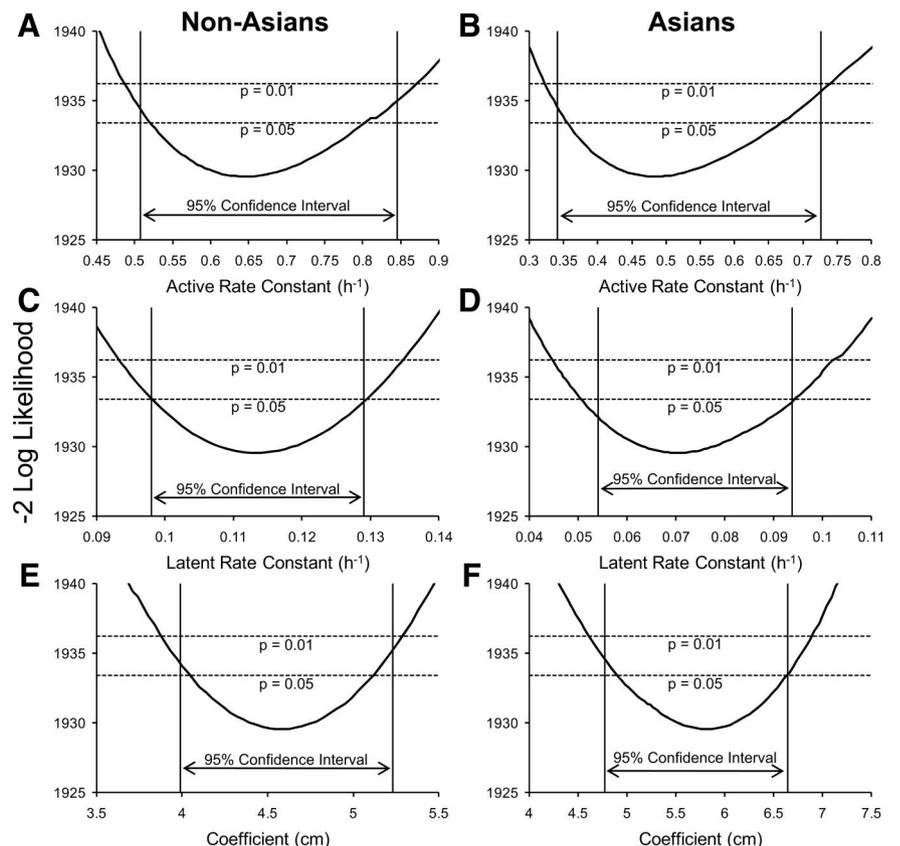


Fig. 4. Log-likelihood profiles: active and latent rate constants and coefficient. Significance estimates calculated on a chi-square distribution (dashed lines) and 95% confidence intervals derived from bootstrap analysis (vertical lines) for (A) active labor rate constant (λ_1) in non-Asian subjects and (B) the active labor rate constant (λ_1) in Asian subjects. (C) The latent labor rate constant (λ_2) in non-Asian subjects; (D) the latent labor rate constant (λ_2) in Asian subjects. (E) The coefficient in the Non-Asian subjects and (F) in Asian patients.

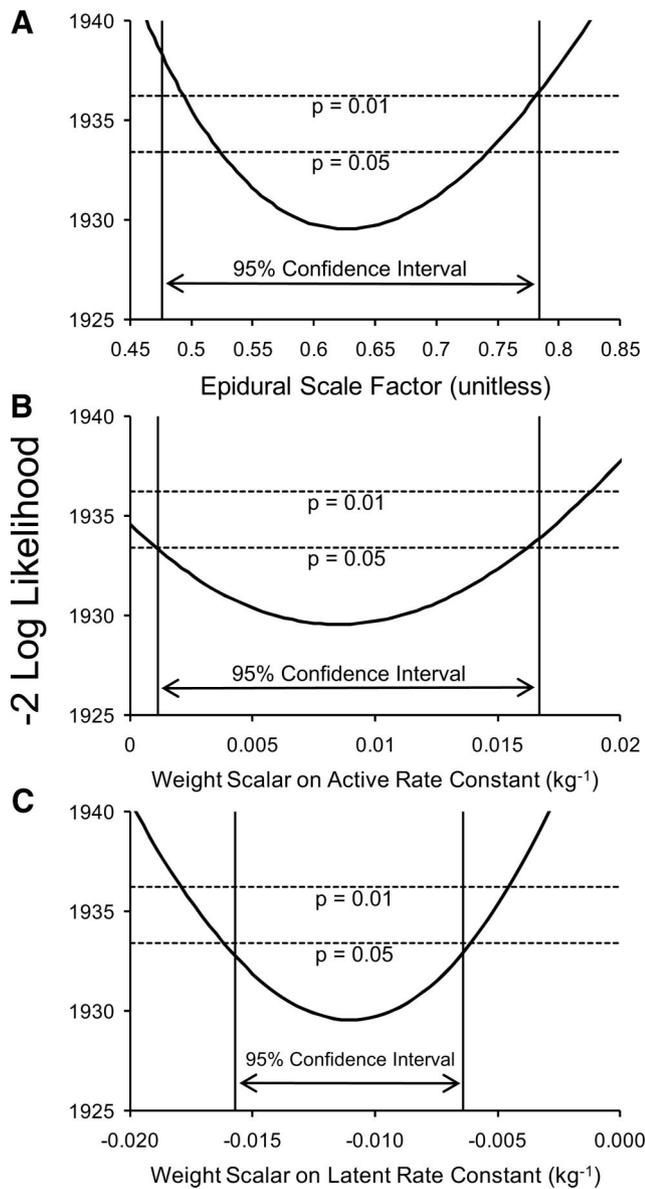


Fig. 5. Log Log-likelihood profiles: epidural and weight factors. Significance estimates calculated on a chi-square distribution (dashed lines) and 95% confidence intervals derived from bootstrap analysis (vertical lines) for (A) epidural scale factor, and the effect of weight on the (B) active and (C) latent rate constants.

table 4 represent the incremental improvement, first of incorporating self-identified ethnicity, and then from incorporating dilation rate.

Figure 8 shows the data fits to (A) the initial model without covariates and (B) the final model incorporating self-identified Asian ethnicity and the rate of cervical dilation. In the initial model, there is only one fit; in the final model, the prediction incorporates instantaneous dilation rate and thus is not a simple line. Rather, individual predictions are shown as black. The shallower line represents the Asian predictions.

A single observation is circled in figure 8. This point represents an Asian patient whose NRS pain score was 3

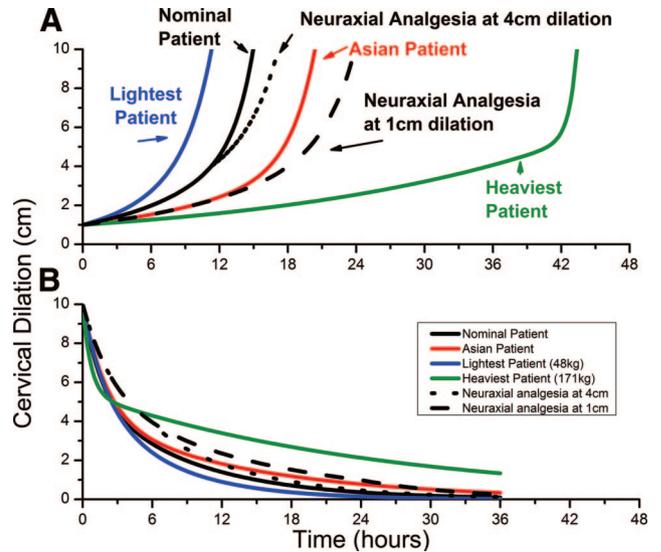


Fig. 6. Effect of individual factors on labor progress. (A) Forward simulations from the labor progression model of the time course required for cervical dilation from 1–10 cm for a “nominal” patient (non-Asian patient of median weight without epidural analgesia), Asian patient (median weight without epidural analgesia), lightest patient (a 48-kg non-Asian patient), heaviest patient (a 171-kg non-Asian patient), and a patient (non-Asian, median weight) with epidural analgesia initiated at 1 cm of cervical dilation or at 4 cm of cervical dilation. (B) Predictions from the labor progression model from full cervical dilation (10 cm) backward through time as actually fit by the model. The X-axis is time before full cervical dilation.

at a predicted cervical dilation of 9 cm and in whom labor had slowed considerably. Removing this observation did not affect the parameters or the statistical significance of the effect of self-identified ethnicity. How-

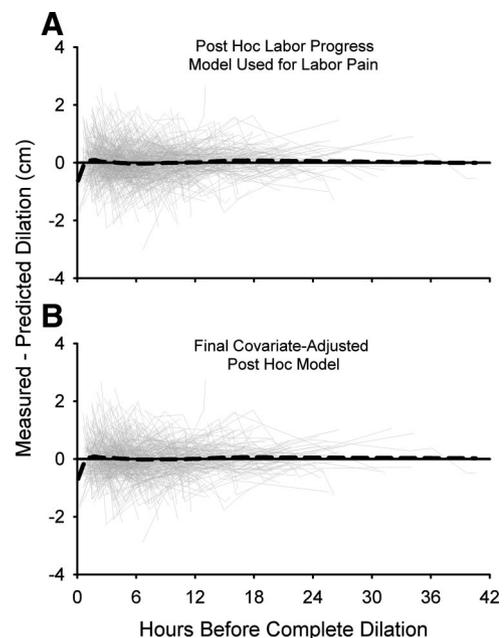


Fig. 7. Model of labor progress. (A) Individual *post hoc* Bayesian fits for the model used to interpolate cervical dilations including epidural effect, and (B) the final *post hoc* Bayesian estimate for the final model incorporating the effect of Asian ethnicity, neuraxial analgesia, and maternal weight.

Table 4. Pain Model

Parameter	Parameter	Intersubject Variability	P Value	95% Confidence Interval
NRS _{MIN} , NRS units	1.0	±495		0.5–1.6
NRS _{MAX} , NRS units	8.7			8.5–9.2
CD ₅₀ , cm	2.3	56%*		2.1–2.6
γ, non-Asian	4.8		0.0003	3.3–5.0
γ, Asian	2.2		0.0003	1.5–3.1
Rate scale on γ	2.3		0.0007	0.0–3.3
Errors				
Median error, NRS units	–0.04			
Median absolute error, NRS units	1.7			

The approximate CV (coefficient of variation), more precisely the standard deviation of the interindividual variability in the log domain.

* SD of intraindividual variability in the log domain (approximate coefficient of variation).

CD₅₀ = the cervical dilation associated with 50% of maximal pain; NRS = numerical rating scale; NRS_{MAX} = the maximal reported pain score; NRS_{MIN} = the minimum reported pain score.

ever, with this point removed, the effect of cervical dilation rate on the model was no longer statistically significant. The point was left in, and the effect of dilation rate was included in the final model because there was no reason to exclude the observation other than identifying it *post hoc* as an outlier.

Figure 9 shows the predicted and measured NRS scores from (A) the initial and (B) final model. The improvement with inclusion of the covariates is nearly invisible. The median absolute prediction error was 1.77 with the initial model, and 1.70 with the final model. As

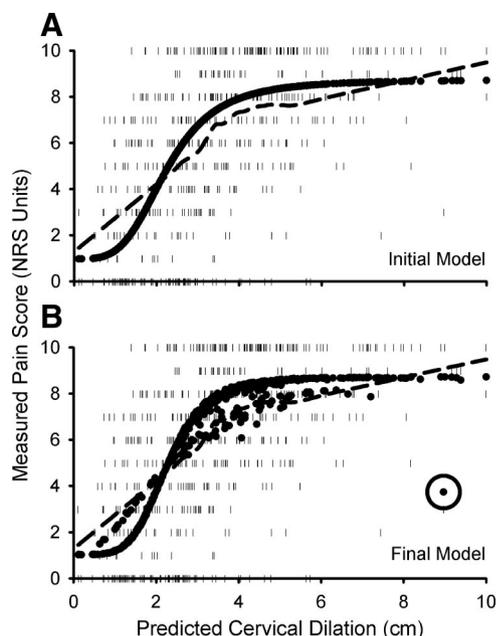


Fig. 8. Pain model. Fits (solid black line) of (A) the initial pain model without covariates and (B) the final pain model incorporating self-identified Asian ethnicity and the rate of cervical dilation. The circled observation represents an outlier and is discussed in the text. The dashed line is a supersmoother through the data. NRS = numerical rating scale.

described for the labor progress model, even though the covariate effects shown in table 4 are highly statistically significant, they represent trivial improvements in the model.

Figure 10 shows the log likelihood profiles and bootstrap analysis for the parameters of the labor pain model. They notably do not have the smooth parabolic shape of the log likelihood profiles in the labor progress model, reflecting the influence of the steep slope that is sensitive to starting estimates. The curves initially had considerable jaggedness, which is still shown by a representative notch in the NRS_{MAX} profile. These proved to be an artifact of NONMEM's inability to fully explore the parameter space, were addressed by calculating log likelihood profiles dozens of times, and selecting minimum values that represented the true minimum (or, at least, as close to the true minimum as NONMEM could identify). The 95% confidence intervals from the bootstrap analysis agree well with the log likelihood profiles, with the exception of the rate scalar on γ. The lower bound of the bootstrap analysis was very close to 0, which reflects the dependence on that parameter on a single point, circled in figure 8. Indeed, this is a demonstration of how the bootstrap shows robustness of a parameter estimate relative to the data, whereas the log likelihood profile shows the robustness of the parameter estimate relative to the model.

Figure 11 shows the error in (a) the final population pain model and (b) the final *post hoc* Bayesian individual pain model. The dashed line snaking through the center of the figure is a supersmoother (a moving average,⁹ implemented in the R programming language). A bias is evident in the population fit (upper graph) at cervical dilations less than 3 cm. This is related to the prediction of the "typical" baseline NRS pain score of approximately 1, which results in an asymmetric distribution of the prediction error; patients can have pain that is 9 points higher than the prediction for a typical individual, but only one point lower than the prediction for a typical individual. Once the cervix has dilated to 3 cm, the model predicts a pain score of 5 in the typical individual, and error in the prediction becomes symmetric. The bias is not seen in the predicted pain scores for individual patients (b) because the model for each individual adjusts the predicted pain score when the cervix is not dilated to the actual level of pain when the patient entered the study. The median absolute residual error was 1.7 NRS points for the population model, and 0.95 NRS points for the individual *post hoc* Bayesian model. The difference between the models shows the magnitude of the still unexplained intersubject variability.

Discussion

Labor is a dynamic process. The biexponential model of labor progress introduced in this paper is a continu-

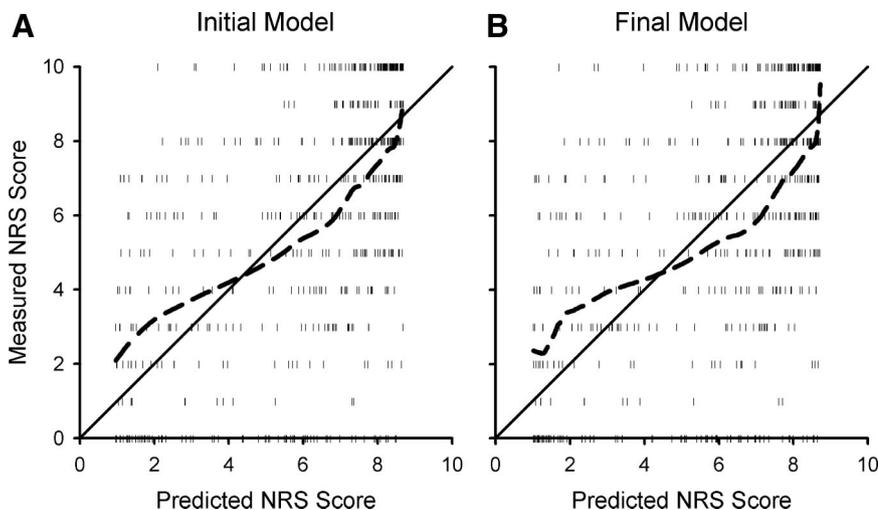


Fig. 9. Predicted and measured NRS scores. (A) Initial and (B) final pain model incorporating the effect of Asian ethnicity and the rate of labor. The *dashed line* is a supersmoother through the data. NRS = numerical rating scale.

ous model suitable for hypothesis testing. The combination of the biexponential labor progress model with our previously described sigmoidal model of labor pain¹ permitted testing the influence of the patient covariates self-identified ethnicity, maternal age, maternal weight, maternal height, birth weight, and gestational age on labor progress and pain. Examining the labors of 500 consecutive nulliparous parturients from 5 self-identified ethnicities, we found that ethnicity and other demographic variables impart highly significant differences in

labor progress and labor pain. However, the magnitude of the effects of patient covariates is quite small and is unlikely to have great clinical significance. Our findings do not suggest that targeting a specific self-identified ethnicity is important to reduce variability in future prospective trials of labor pain.

The racial and ethnic identities recorded by our hospital were recommended for use in the 2000 census, where participants were asked to chose one or more of the following categories: American Indian or Alaska Na-

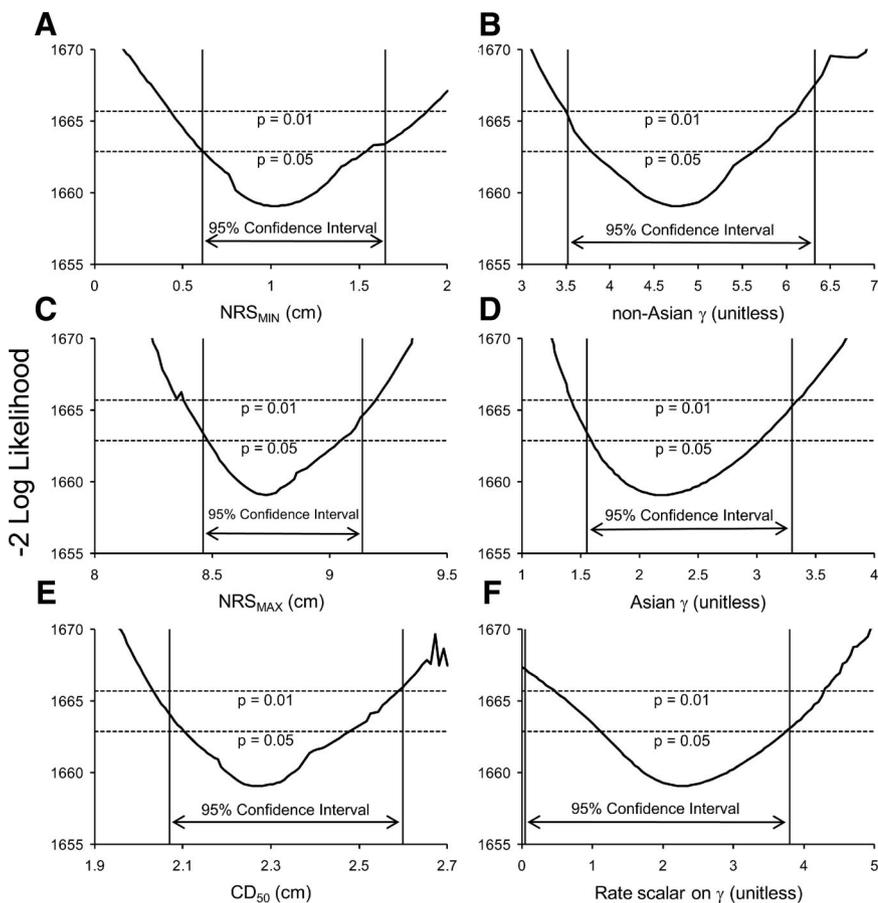


Fig. 10. Log-likelihood profiles: Pain Model. Significance estimates calculated on a chi-square distribution (*dashed lines*) and 95% confidence intervals derived from bootstrap analysis (*vertical lines*) for the parameters of the labor pain model. (A) NRS_{MIN} for all subjects, (B) Non-Asian γ -slope function, (C) NRS_{MAX} for all subjects, (D) Asian γ -slope function, (E) CD_{50} for all subjects, and (F) the rate scalar on γ . NONMEM had considerable difficulty calculating the log-likelihood profiles, requiring a local minimum function to remove some of the jaggedness from several curves. The retained jaggedness in the curve for CD_{50} is representative of the unsmoothed curve. CD_{50} = the cervical dilation associated with 50% of maximal pain; NRS = numerical rating scale; NRS_{MAX} = the maximal reported pain score; NRS_{MIN} = the minimum reported pain score.

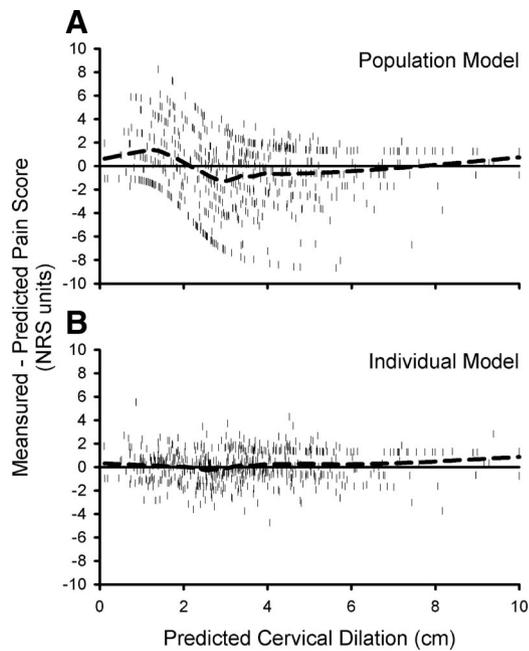


Fig. 11. Error: Pain Model. (A) Initial population pain model and (B) final *post hoc* Bayesian individual pain model that incorporates the effect of Asian ethnicity and labor rate. The dashed line snaking through the center of the figure is a supersmoother. NRS = numerical rating scale.

tive; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; and White.” Participants were also asked to choose an ethnicity between Hispanic and non-Hispanic. Our patients were only allowed the choice of one group, or they were placed in the group called “Other.” There are very few patients who report American Indian, Native Alaskan, Native Hawaiian, or Pacific Islander background; therefore, these patients were also grouped with the subjects in the “Other” group. This was the only information available to us, so conclusions must be limited to these self reported groups; we can say little about the role of culture and genetics on pain sensitivity.

The “Asian” category is not homogenous; it reflects the considerable ethnic diversity of Asia. Our findings of slower labor and less pain may be driven by a particular subgroup in the Asian population. Our methodology would be appropriate for similar studies in maternity wards in Asia to discern subtle effects of subgroups within an Asian population.

The progression of labor may be affected by psychosocial, emotional, physical, and environmental factors.¹⁰ In contrast to our findings, a large retrospective cohort study from University of California, San Francisco, did not identify a difference in the first stage of labor according to ethnicity. However, their methods differed from ours in that they did not study the latent and active labor separately; they only considered the length of the first and second stages of labor together.⁵ Our findings demonstrate the enhanced model sensitivity imparted by considering each cervical exam rather than just the total

time before delivery. Potentially consistent with our findings, Greenberg *et al.* found that both nulliparous and multiparous Black women had a shorter second stage of labor when compared with White women, whereas Asian women experience a longer second stage of labor and higher Cesarean section rates.^{5,11} It is possible that the slower rate of labor in Asians in the active phase may contribute to Cesarean sections for failure to progress. All subjects screened for this study had a vaginal delivery; as such, we do not know whether our Asian and White patients had a higher Cesarean section rate. It is likely that our results are biased to some extent by limiting our population to women who delivered their children vaginally.

We did not study other patient covariates related to ethnicity, such as the country in which a woman was raised, the ethnicity of the partner, the patient’s language, educational status, or attendance at labor educational programs. We do not consider it likely that these covariates would explain the large unexplained intersubject variability in labor progress and labor pain, given the very modest effects of self-identified ethnicity. The more productive line of investigation, in our view, will be to look for genetic polymorphisms that correlate with labor pain and progress.

The rates of both active and latent labor in our cohort are slower than those described by Friedman for nulliparous patients.¹² Several authors have documented this historical change.^{13,14} Population demographics and the medical management of labor have changed markedly in the years since Friedman reported his results. Particularly, the induction of labor is common, and use of oxytocin has increased and represented 27% and 60% of our sample respectively. While labor induction and oxytocin use did not vary according to ethnicity, it might account for the overall slower progress of labor compared to historical data. The mothers in our study are older and heavier than previously.^{15,16} In our sample, high maternal weight was predictive of slower labor (fig. 6). This association has been noted previously and may contribute to a higher risk of Cesarean delivery in obese women.^{15,16} There may be a direct effect of obesity on the myometrium. Myometrium from obese women taken at Cesarean section contracted with less force and frequency and had reduced calcium transients when compared with uterine tissue from lean women.¹⁷

We found that the placement of neuraxial analgesia was associated with a decreased rate of labor progress (fig. 6). In retrospective studies, neuraxial analgesia has often been associated with slower labor and a higher rate of Cesarean delivery.¹⁸ This has typically not been validated in prospective, randomized controlled studies, which suggests that the relationship between neuraxial analgesia and labor slowing is not causal.^{19–23} In addition, studies have correlated early severe labor pain with dystocia^{24–26}; as a result,

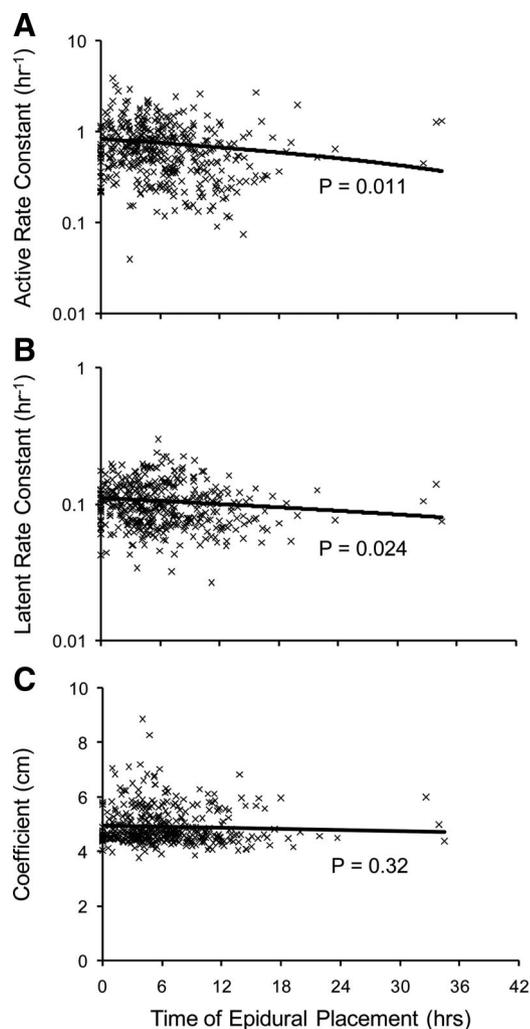


Fig. 12. Time of epidural placement and rate of labor progress. (A) active rate constants (λ_1), (B) latent rate constants (λ_2), and (C) the coefficient (C) as a function of the time of neuraxial analgesia initiation. The slope is significantly different from 0 for λ_1 (** $P < 0.01$) and λ_2 (* $P < 0.05$), suggesting that patients with slower labors are given neuraxial analgesia earlier in labor.

a temporal association of neuraxial anesthesia with slowed labor is an expected finding.

The retrospective design of our cohort study imposes significant limitations on consideration of causality. However, our model of the neuraxial analgesia effect permits a modest exploration of causality. In each patient, we estimated the parameters of labor: the active rate constant, the latent rate constant, and the coefficient. As described in the appendix, the model incorporated the effect of neuraxial analgesia as a scalar on time (X axis). If the model accurately captures the biologic effect of epidural anesthesia, then the active rate constant, the latent rate constant, and the coefficient estimated by NONMEM are the values as though neuraxial analgesia had never been placed. As shown in figure 12, earlier initiation of neuraxial analgesia (greater time) is associated with lower values of the active and latent rate constants, at $P = 0.011$ and $P = 0.024$, respectively.

Thus, patients with slower labor (smaller rate constants) received earlier neuraxial analgesia. These data are consistent with, but do not prove, the association of neuraxial analgesia placement with slower labor progress is not causal.

Demographic variables were comparable among groups, except for employment, marital status, and primary language. These variables showed no correlation with labor pain or progress. The interventions used in labor management, including analgesia and oxytocin were also similar among groups, suggesting that there were no systematic differences in treatment based on ethnicity in our population. Previous studies have suggested that differences in Cesarean section rates between Black and White women is related to variability in birth weight.⁶ However, we did not observe an association between birth weight and the rate of labor progress.

Asians report less labor pain and have a slower active phase of labor; it is possible that both outcomes may relate to having weaker contractions. In some cases, factors that increase contractility such as oxytocin and placental abruption are also associated with more reported pain.^{1,6} Instantaneous labor rate was a significant covariate for labor pain in our study. Although logical and apparently valid, the statistical significance of this finding was dependent on the data from a single Asian patient who had a slow labor and little pain and as such should be taken with caution.

The relationship between ethnicity and other types of pain has been studied in the past.^{27,28} Previous studies have shown differences among ethnic groups with respect to stoicism, healthcare quality, and pain coping strategies. Prepared childbirth and breathing techniques have been shown to reduced pain scores in early labor.^{2,29} We do not know which patients had professional childbirth preparation; as such, we cannot determine whether this variable contributed to the difference that we have identified.

Our study found that the Asian group reported slightly less painful labor, whereas the Black, Hispanic, and Other groups reported more pain when compared to all patients in other groups. The White patients could be grouped with the Asians if rate were not taken into account. However, even when the Asian group's slower rate of labor is accounted for, the Asian group still reported less pain than all other patients. Between 3 to 5 cm cervical dilation, there is at least 1.5 NRS difference between the Hispanic-Black-Other groups compared with the Whites-Asian groups. Most epidural anesthetics were administered when the patient had 3–5 cm of cervical dilation. The anesthesiologist might encounter positioning and patient cooperation issues when initiating epidural anesthetics in patients with more pain. Average cervical dilations at epidural analgesia request for the five ethnic groups were not different but the NRS scores varied, suggesting that a more active ap-

proach to pain management might be considered in selected groups.

Interpretation of our results is limited by the fact that the subjects included in the study were from incompletely overlapping time periods. We do not believe that there were any major alterations in obstetrical or nursing protocols during this time period; as such, we do not believe significant bias is introduced. Ninety-four percent of women in our population received analgesia during their labor. As such, there are fewer NRS scores in late labor because we did not consider pain scores after analgesia initiation. As no parturient reported a decrease in pain during labor in the absence of analgesia, women who reported high pain scores in early labor and then requested analgesia would likely have continued to have high pain scores throughout labor. As such, we have likely underestimated NRS_{MAX} . There was little variability in NRS_{MAX} . All subjects without analgesia reported significant pain close to full dilation. As such, in our final model we fixed intraindividual variability at 0 on this term. Similarly, it is possible that women having a very rapid painful labor would be more likely to be rushed to a labor room and have an epidural placed before the nurse could take a pain score with their admission exam. As such, pain might be underrepresented. The impact of the frequent use of epidural analgesia in our population can be evaluated with a similar study in a population with lower use of epidural analgesia. Similarly, the interpretation of our data are affected by informed censoring, in that patients with higher levels of pain are more likely to receive epidural analgesia and have censored observations. Fortunately, a mixed effects approach is fairly robust, even in the presence of informed censoring.³⁰

We only have access to pain reports after arrival to the hospital. One reason for coming to the hospital is pain. Women with more pain likely arrive earlier. We might have a greater representation of higher pain scores in early labor. However, this should not confound our analysis of ethnicity as the cervical exam on hospital arrival did not vary among ethnic groups. A prospective study of labor pain with NRS scores starting in earlier labor would help to clarify this issue.

Evidence-based medicine applies the best current evidence in making decisions to guide the care of the individual patient. The practice of pain management in obstetrical anesthesia should be individualized to the needs of each patient. We identified significant variability in both the rates of labor progress and the pattern of labor pain report. However, only a small portion of this variability is explainable by consideration of demographic variables including ethnicity. The rest of the variability may yet be explained by genetic or environmental factors that we have not considered.

No model can be a “final model.” Our models of labor progress and pain are the best that we could achieve with the currently available data. We have used our

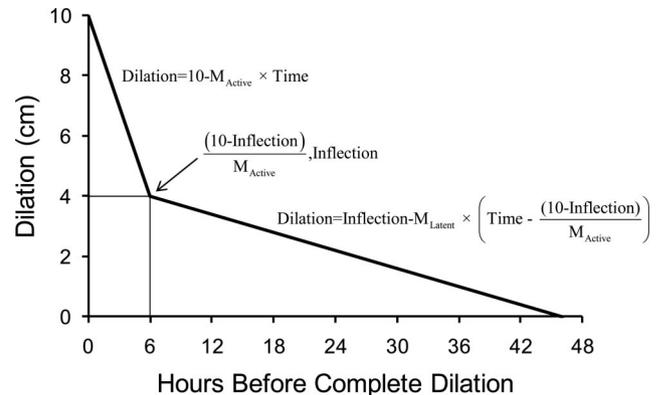


Fig. 13. Traditional bilinear model of labor progress. The active phase of labor is described as $Dilation\ (cm) = 10 - M_{Active}(\text{time}\ [h])$. The transition point between active and latent labor, $I = (10 - \text{cervical dilation at transition}\ [cm]) / M_{Active}$. The latent phase of labor is described as $Dilation\ (cm) = I - M_{Latent} \left(\text{Time} - \frac{(10 - \text{Inflection})}{M_{Active}} \right)$.

model to carefully examine the effect of several demographic and labor management-related variables on the progress and pain of labor. Several covariates had highly statistically significant effects, but the effects explained a very small part of intersubject variability in labor progress and pain. Future studies might find that genetic polymorphisms were more important covariates of labor progress and labor pain than the covariates we explored. We have provided our data and the details of our models as Supplemental Digital Content in the hope that other investigators will find it useful for testing hypotheses that may go further to explain the extensive biologic variability.

Appendix: Population Model of Labor Progress

Friedman originally modeled labor progress as a sigmoidal relationship,^{8,12} which was later simplified to a model of two straight lines. The first line is used to describe latent labor, where the cervix dilates at approximately 0.2–0.5 cm/h. The second line describes active labor, where the cervix dilates at 1–2 cm/h. Traditionally, women have been considered to transition from latent to active labor when the cervix is dilated to approximately 4–5 cm.

Figure 13 shows a bilinear model that captures this structure, consisting of two intersecting straight lines. As is usually the case with labor progress models, time runs backwards along the X axis, with 0 being the time of full dilation. The bilinear model has three parameters, M_{Latent} , the rate (slope) of latent labor, M_{Active} , the rate (slope) of active labor, and $Inflection$, the cervical dilation where women transition from latent labor to active labor. The time of the transition from latent to active labor (*i.e.*, the time when the curves intersect) can be readily calculated as $(10 - \text{Inflection}) / M_{Active}$. The bilinear model is necessarily bounded at 0 and 10, as cervical dilation cannot be negative, and full dilation is defined as 10 cm.

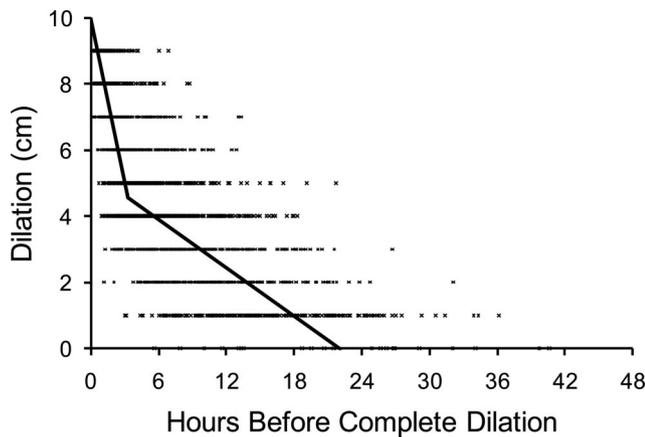


Fig. 14. Population fit of bilinear model of labor progress.

Using NONMEM, we estimated the parameters of the bilinear model from the cervical dilation data in all patients. We estimated both intersubject and intrasubject variability with additive error models. We also used the “first order” method because the “first order conditional estimation” method failed to run. The parameters for each individual patient were estimated using the *post hoc* step. The population fit of the bilinear model to all of the data are shown in figure 14. There is a considerable amount of variability about the typical prediction, with a median absolute error, $|(measured\ dilation - predicted\ dilation)|$, of 1.0 cm. The goodness of fit is shown in figure 15 for the population estimate (A) and the individual *post hoc* Bayesian estimates (B). The -2 log likelihood function for the bilinear model is 2741.

Figure 16 shows log likelihood profiles for the three parameters of the bilinear model, the latent slope (A), active slope (B), and inflection point (C). The log likelihood profiles reveal a profound sensitivity of the model to initial parameter estimates, with small changes in the initial estimates resulting in fluctuations in -2 log likelihood of nearly 200 points. This instability is caused by the bilinear model itself, which has an abrupt change at the intersection of the two lines (*i.e.*, at the transition from latent to active labor). Consider an observation

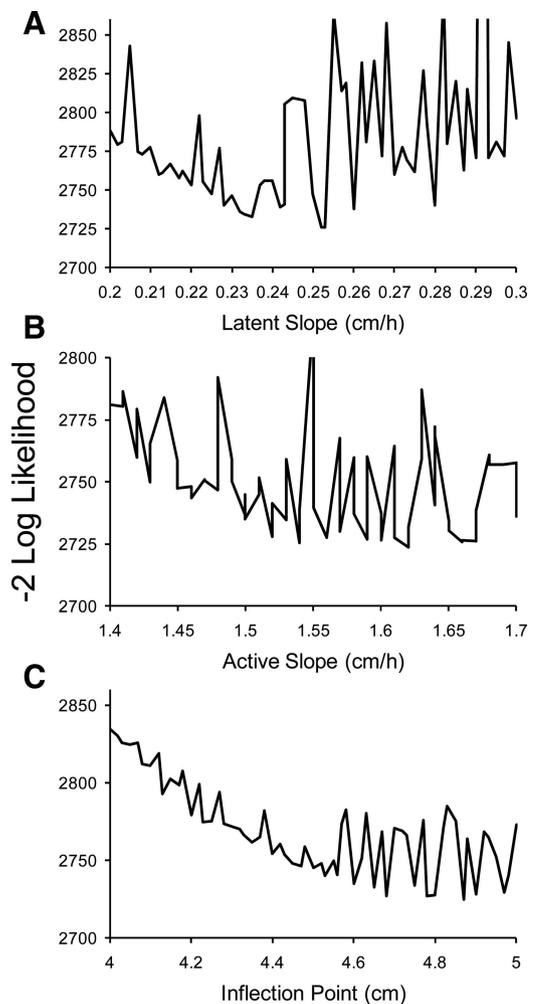


Fig. 16. Log likelihood profiles for the bilinear model of labor progress. (A) Active rate (cm/h), (B) latent rate (cm/h), and (C) inflection point (cm).

immediately to the left of the transition point. A change in either slope, or in Inflection, might move the transition point so that the observation is now to the right of the transition. Suddenly, this data point is being fit to an entirely different line, with unpredictable results. The lack of a smooth transition (or, more precisely, the lack

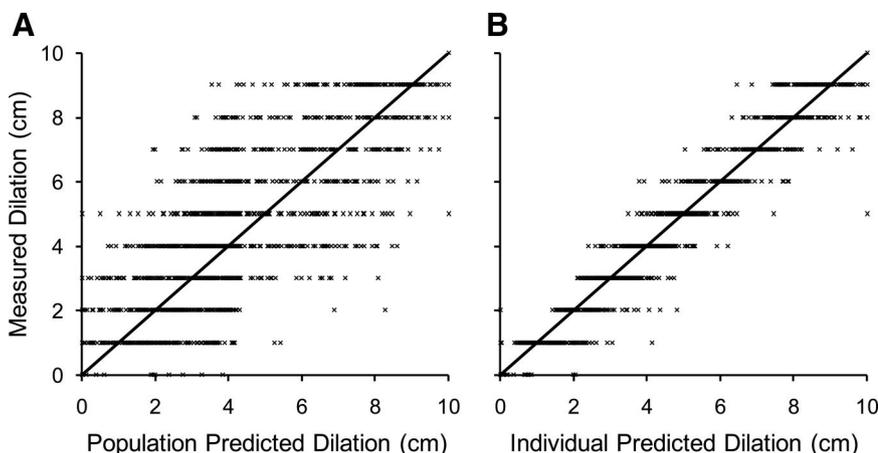


Fig. 15. Goodness of fit: Bilinear model of labor progress. (A) Population estimate and (B) Individual *post hoc* Bayesian estimate.

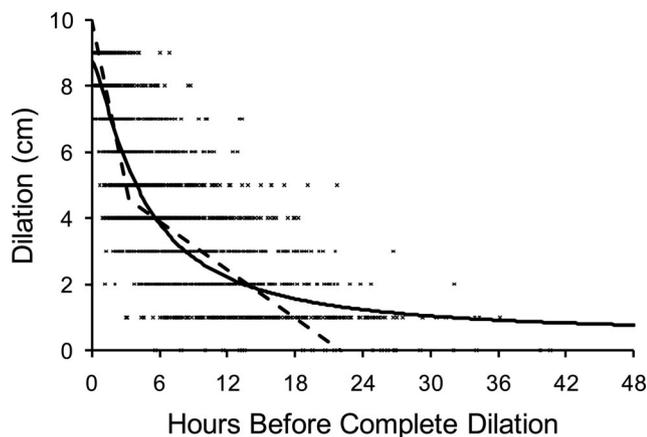


Fig. 17. Comparison of bilinear model to sigmoidal model. Dashed line represents bilinear model and solid line is sigmoidal model,

$$\text{Dilation} = CD_0 + (CD_{\min} - CD_0) \frac{\text{Time}^\gamma}{\text{Time}_{50}^\gamma + \text{Time}^\gamma}$$

of a derivative at the transition point) makes the model profoundly sensitive to starting estimates. This profound sensitivity to starting estimates preclude use of the model for hypothesis testing. The bounding of the model at 0 may also contribute to the instability of the model, as the derivative is undefined for all points to the right of the intersection of the line for latent labor with the X axis.

Figure 17 compares the linear model to a sigmoidal model, similar to Friedman’s original model, estimated with NONMEM by using the function

$$\text{Dilation} = CD_0 + (CD_{\min} - CD_0) \frac{\text{Time}^\gamma}{\text{Time}_{50}^\gamma + \text{Time}^\gamma},$$

where CD_0 is the cervical dilation at time 0 (typically 10 by definition), CD_{\min} is the minimal cervical dilation (which should be 0, but because women arrive at the hospital somewhat dilated was 0.43 cm in the final model), Time is the number of hours before full dilation, Time_{50} is the time of half dilation, and γ is the steepness of the transition. The model follows the data better than the simple bilinear model, as suggested by the -2 log likelihood of 2,499, a decrease of 242 points from the log likelihood for the bilinear model. The sigmoidal model provides for a terminal deceleration in labor progress, which is not evident in the raw data, is virtually invisible in the function, and has been disputed by several investigators.^{13,31}

The data suggest another model. The solid line in figure 18 is a supersmoother function (a moving average,⁹ implemented in the R programming language) applied to the data. The best bilinear fit appears as the dashed line. The supersmoother curve suggests a biexponential model, which we implemented with the function $\text{Dilation} = Ce^{-\lambda_1 t} + (10 - C)e^{-\lambda_2 t}$. This function has the same number of parameters as the model with two

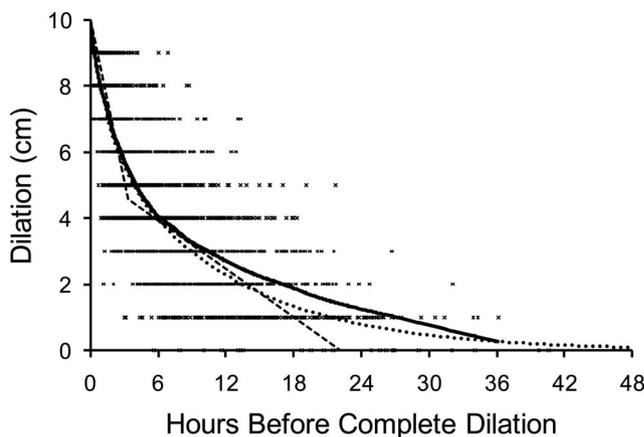


Fig. 18. Comparison of bilinear model to final biexponential model. Dashed line represents bilinear model, solid line is a supersmoother similar to a moving average, and the dotted line is the biexponential model, $\text{Dilation} = Ce^{-\lambda_1 t} + (10 - C)e^{-\lambda_2 t}$, where γ_1 is the rate constant for active labor, γ_2 is the rate constant for latent labor, and C is the number of centimeters associated with active labor. As such, $10 - C$ is the cervical exam at which latent labor transitions to active labor.

intersecting lines. λ_1 and λ_2 are rate constants, with units of inverse time. During latent labor, cervical dilation will double every $0.693/\lambda_2$ hours. During active labor, cervical dilation will double approximately $0.693/\lambda_1$ hours. C can be thought of as approximately the number of centimeters of dilation associated with the active phase of labor. Therefore, $10 - C$ is approximately the number of centimeters of dilation associated with the latent phase of labor, and represents the transition point between latent and active labor. The transition from latent to active labor occurs gradually; therefore, it is probably best to not focus on the value of C or the specific exponents, but rather to consider the function in its entirety. The rate of cervical dilation is the derivative of $\text{Dilation} = Ce^{-\lambda_1 t} + (10 - C)e^{-\lambda_2 t}$, with respect to time, which can be calculated as $\text{Rate (cm/h)} = C\lambda_1 e^{-\lambda_1 t} + (10 - C)\lambda_2 e^{-\lambda_2 t}$.

Figure 18 shows the fit of the biexponential model to the data (dotted line). Although the visual improvement is not dramatic, the improvement over the bilinear model is considerable from the perspective of NONMEM: a decrease in the -2 log likelihood from 2,741 to 2,416, an improvement of 325 points. The -2 log likelihood of the three-parameter biexponential model is 83 points less than the four-parameter sigmoidal model. Although the models are not nested, and thus cannot be directly compared with the likelihood ratio test, the improvements in -2 log likelihood strongly support the use of the biexponential model to describe the data, as does the visual congruence of the bilinear model with the nonparametric supersmoother curve. For completeness, we also considered a monoexponential curve, $\text{Dilation} = Ce^{-\lambda t}$. This curve produced a -2 log likelihood that was 178 points worse than the biexponential model, and was not further considered.

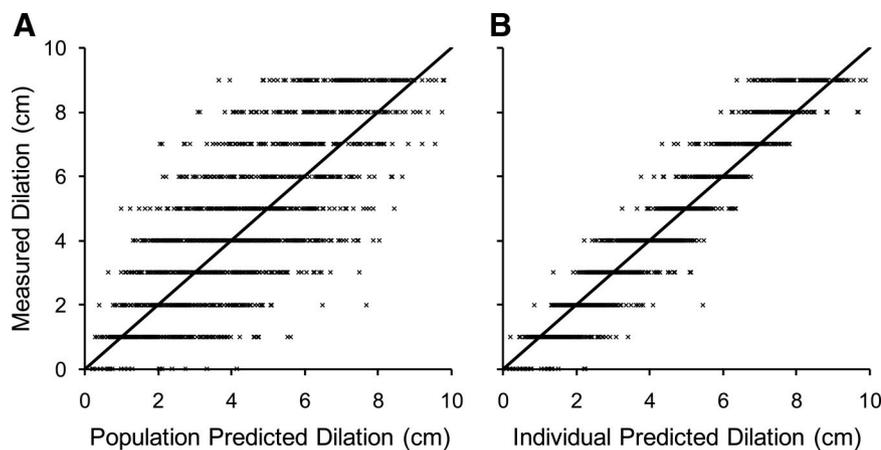


Fig. 19. Goodness of fit: Biexponential model of labor progress. (A) Population estimate and (B) individual *post hoc* Bayesian estimate.

Figure 19 shows the goodness of fit for the population biexponential model (A) and the individual biexponential model (B). The median absolute residual error for the population model is 0.98 cm, indistinguishable from the median absolute residual error of 1.0 cm with the bilinear model.

Figure 20 shows the likelihood profiles for the latent rate constant (A), active rate constant (B), and the coefficient (C). The smooth shape demonstrates the correct behavior for a model useful for hypothesis testing. The dashed lines show the change in the $-2 \log$ likelihood that would justify inclusion of an additional parameter at $P = 0.05$ and $P = 0.01$.

We estimated the 95% confidence for each parameter in the biexponential model by performing 1,000 bootstrap replicates with replacement using PLT Tools. The 95% confidence interval was calculated by using an Excel spreadsheet as the 2.5% and 97.5% values for each parameter from the 1,000 replicates. The 95% confidence intervals for each parameter are included in figure 20. Because of the different methodologies (*i.e.*, each bootstrap analysis considers a resampled population, not the same data set as used in calculating the $-2 \log$ likelihood profile), it is an expected result that the 95% confidence intervals from the bootstrap analysis do not exactly match the intervals suggested by the $-2 \log$ likelihood profiles.

The slope of the biexponential function $\text{Dilation} = Ce^{-\lambda_1 t} + (10-C)e^{-\lambda_2 t}$ can be calculated as the derivative with respect to time: $\text{Rate}(\text{cm}/\text{h}) = \lambda_1 Ce^{-\lambda_1 t} + \lambda_2(10-C)e^{-\lambda_2 t}$. Figure 21 shows the rate of cervical dilation per hour (A) and the rate of dilation as a function of cervical dilation (B).

Given the visual similarity of the biexponential model to the supersmoother curve, the improved quality of the fit of the biexponential model compared to the bilinear model (325 points) and sigmoidal model (83 points), the stability demonstrated in the likelihood profiles, and the confirmation of the approximate confidence intervals using bootstrap analy-

sis (fig. 20), we used the biexponential model for testing the relationship among self-identified ethnicity, labor progress, and labor pain.

We considered two types of covariates in the analysis: time invariant covariates (covariates that did not change over the course of labor) and time variant covariates (covariates that occurred during the labor). The time invariant covariates were patient age, weight, height, gestational age, birth weight, and self-reported ethnicity. We modeled the time invariant covariates as simple linear adjustments to λ_1 , λ_2 , and C.

The time variant covariates were institution of epidural anesthesia, an oxytocin infusion, labor induction, and rupture of membranes. We could not model these as simple linear adjustments to λ_1 , λ_2 , and C; that approach would produce two distinct curves, with an abrupt discontinuity in predicted cervical dilation at the moment of transition. We could have used a mathematical function to constrain the model to a smooth function at the moment of a time-varying covariate, but we could find no precedent for that approach nor an intuitively tractable mathematical model. Instead, we adopted a very simple approach that ensured a smooth transition. We introduced a "time adjustment" factor that accelerated (or decelerated) the time axis at the transition moment. This required introducing only a single term, which represented how the time-varying covariate accelerated (factor > 1) or decelerated (factor < 1) the progress of labor. The factor, θ , was defined as the time interval from the moment of the intervention until 10 cm of dilation in the absence of the intervention divided by the time interval from the moment of the intervention until 10 cm of dilation in the presence of the intervention. To express it more formally, let T_{Observed} be the actual time between the intervention and full dilation (which is the same as the time of the intervention) and $T_{\text{NoIntervention}}$ be expected time if the person had not had the intervention. We define the

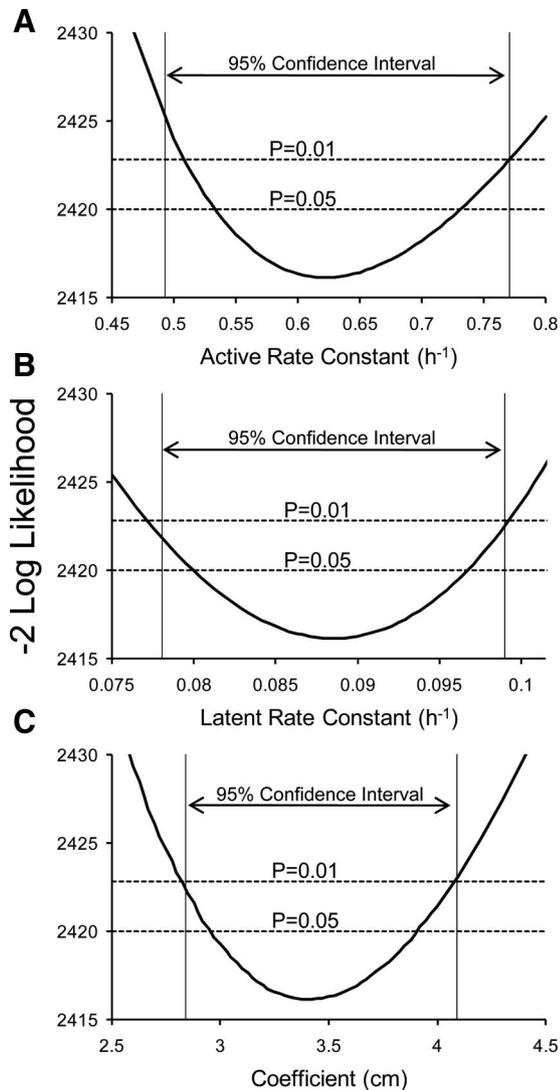


Fig. 20. Log likelihood profiles for the biexponential model of labor progress. (A) Active rate constant, γ_1 (hr^{-1}), (B) latent rate constant, γ_2 (hr^{-1}), and (C) the number of centimeters associated with active labor. Solid vertical lines represent 95% confidence intervals calculated with bootstrap, and the dashed lines are 95 and 99% confidence intervals calculated with Excel.

time scale factor, θ , as:

$$\theta = \frac{T_{\text{NoIntervention}}}{T_{\text{Observed}}}$$

If $\theta < 1$, then T_{Observed} is greater than $T_{\text{NoIntervention}}$, and labor is slowed. For example, $\theta = 0.6$, then labor runs at only 60% of the expected pace after an intervention. If $\theta > 1$, then T_{Observed} is less than than $T_{\text{NoIntervention}}$, meaning that labor is accelerated by the intervention. For example, if $\theta = 2$, then the pace of labor is doubled following the intervention.

The labor model is represented as a biexponential function of time, t . The model runs backwards in time, with $t = 0$ representing the time of full dilation. Any intervention scales the time axis from the moment of the intervention until full

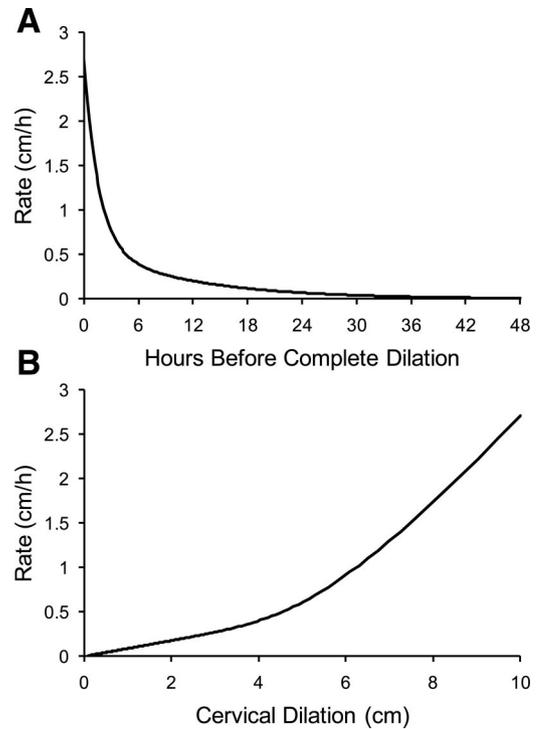


Fig. 21. Instantaneous rates of labor progress (A) by time (h) and (B) by cervical dilation (h).

dilation, which is when $t = 0$. Thus, the presence of an intervention such as epidural placement requires recalculation of all values of t to reflect the acceleration or deceleration of labor. This requires the introduction of two terms, t_{unscaled} , which is the time recorded in the study, and t_{scaled} , which is a scaled time that has expanded or contracted from the intervention, and is the value of time used in the labor progress model. The calculation of t_{scaled} can be derived from the definition of θ .

Before the intervention, t_{scaled} must include the full impact of the intervention on the time course. Based on the definition of θ , $T_{\text{NoIntervention}} = \theta \times T_{\text{Observed}}$. The full impact is the difference between the observed time, T_{Observed} , and the expected time in the absence of the intervention, $\theta \times T_{\text{Observed}}$. Thus, $t_{\text{scaled}} = t_{\text{unscaled}} + \theta \times T_{\text{Observed}} - T_{\text{Observed}} = t_{\text{unscaled}} + T_{\text{Observed}}(\theta - 1)$.

At the moment of the intervention, $t_{\text{scaled}} = T_{\text{NoIntervention}}$, and $t_{\text{unscaled}} = T_{\text{Observed}}$. By the definition of θ $T_{\text{NoIntervention}} = \theta \times T_{\text{Observed}}$; therefore, at the moment of the intervention $t_{\text{scaled}} = t_{\text{unscaled}} \times \theta$. This relationship holds after the intervention as well: $t_{\text{scaled}} = t_{\text{unscaled}} \times \theta$.

Figure 22 shows the effect of the model. The top figure 22A, in which time goes forward, shows the effect of an epidural placed at 16 h and $\theta = 0.66$. The course of labor is abruptly slowed from that time of epidural placement, so that the woman reaches full dilation approximately 4 h later than had the epidural not been placed. The lower figure 22B represents the data as seen from the model, in which time runs backwards from the point of full dilation. Only 24 h of labor is shown. The woman with the

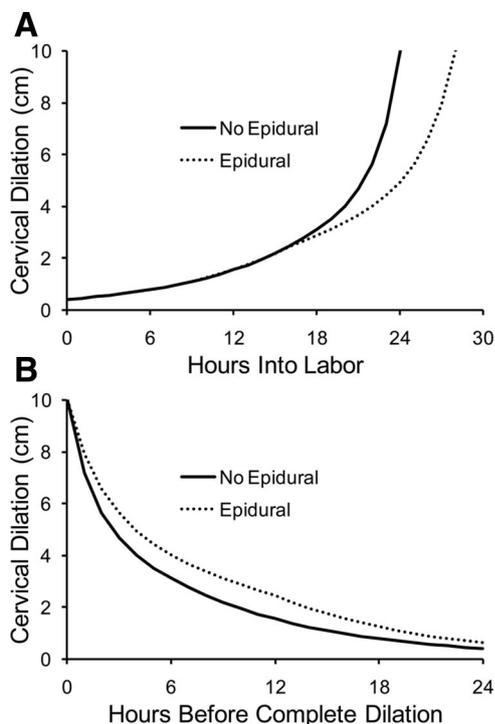


Fig. 22. Effect of time variant covariate on labor progress. Covariate effects that occur during labor are considered as time scalars where $T_{\text{NoIntervention}} = \theta \times T_{\text{Observed}}$. (A) Time proceeds forward, and an epidural is placed after 16 h of labor. (B) Time proceeds backward, and an epidural is placed 12 h before complete cervical dilation. $\theta = 0.66$ in these examples; in the presence of an epidural, time proceeds at 66% of the rate that it does without an epidural.

epidural undergoes less dilation during those 24 h than the woman without the epidural. Note that the top and bottom figures show the same data, but they line up at differing points, with time running backwards in the lower figure.

The parameters of the models explored in this appendix were estimated by NONMEM by using the “first order” method. This was necessary because the extreme sensitivity of the bilinear model to initial estimates precluded using the “first order conditional estimates” approach. In this way, the appendix compares models estimated with exactly the same methodology. This differs from the model development in the article text, where only “first order conditional estimates” were used.

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