

Evidence Synthesis where the Data are on very Complex Functions of the Parameters: Using WBDev

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Evidence Synthesis (1)

- Statistical combination of data from different studies
 - Summary effect measures
 - With uncertainty
- E.G. Meta-Analysis
 - ... but more general
 - data can tell us about functions of parameters, and different studies may report different outcomes
- Health Technology Appraisals (e.g. bodies such as NICE in the UK)

Evidence Synthesis (2)

- “All Available Evidence”
 - Capture an accurate view of uncertainties
 - Decision analysis / Research prioritisation
- But can mean some (or all) data do not directly give parameters of interest
- Rather, the data estimate (sometimes very complex) functions of parameters

Modelling Framework

- Bayesian approach natural
 - Decision context
 - Single unified analysis
 - Propagation of uncertainties into decision model
 - Flexibility of MCMC/WinBUGS

Modelling Issues

- WinBUGS
 - slow to compile & run when relationships between data and parameters very complex
- Could re-parameterise
 - ... but often there's a natural parameterisation on which to specify priors and on which we want inference
- WBDev (Lunn 2004)
 - Provides an efficient way to hard-wire code

Outline

- Give two examples where the data provide information on functions of the basic parameters
 - Asthma state transitions
 - Early Onset Group B Streptococcus (EOGBS) infection in infants
- Investigate the advantages of using WBDev to hard-wire functions representing these functional relationships

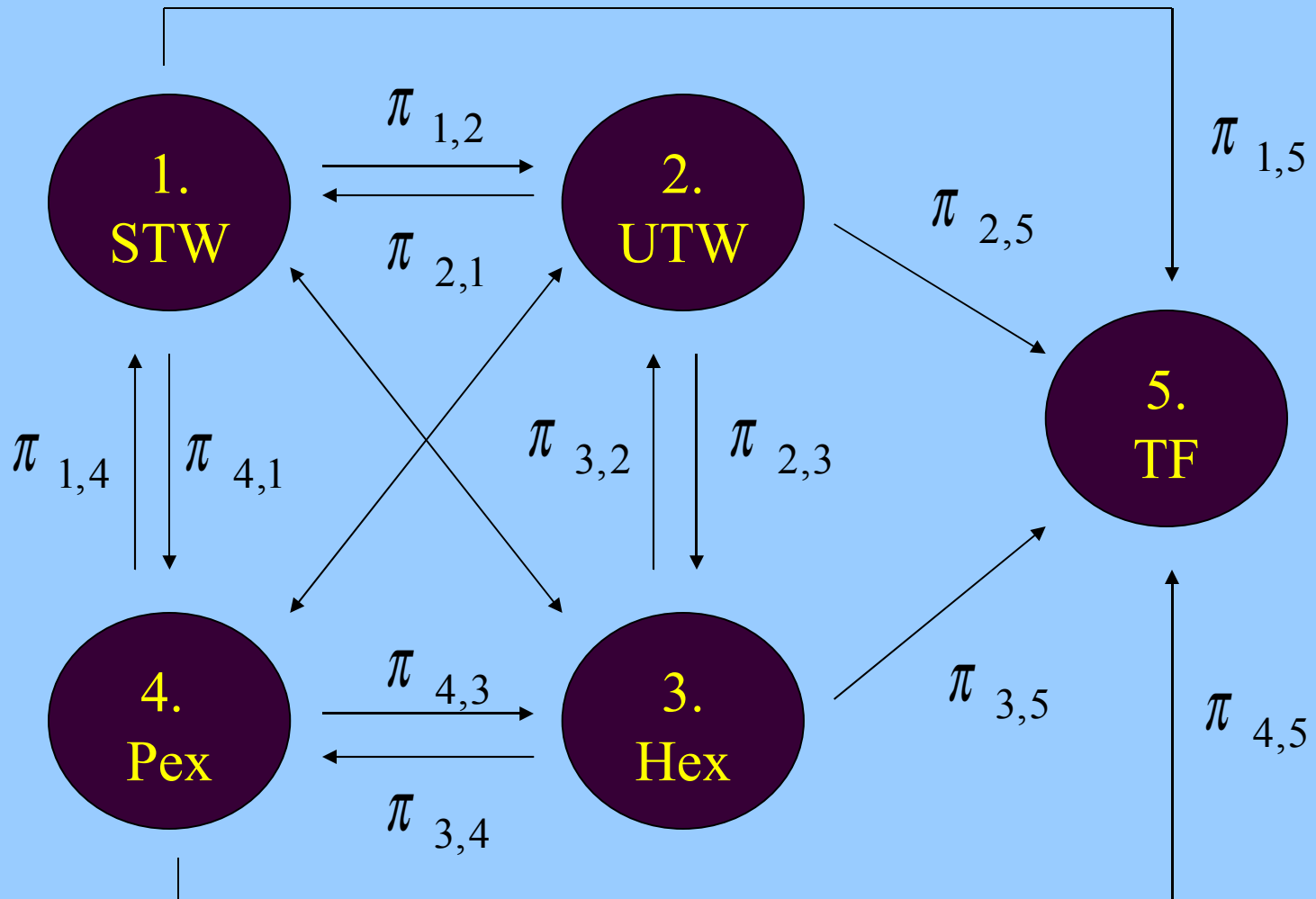
Motivation for Asthma Example

- A colleague (Aicha Goubar) working on an HIV infection/behaviour change
 - Markov model with 13 states
 - Data on state at end of year
 - But monthly transitions are basic parameters
 - Complex relations between model and the data
- Here we illustrate the issues with a far simpler artificial set of data with the same basic features

Asthma State Transitions (Briggs et al 2003)

- Discrete Time Markov Model
- 5 Health States:
 - State 1: Successfully Treated Week (STW)
 - State 2: Unsuccessfully Treated Week (UTW)
 - State 3: Hospital treated exacerbation (Hex)
 - State 4: Primary care treated exacerbation (Pex)
 - State 5: Treatment Failure (TF) ... absorbing

Markov Model



Asthma State Transitions

- Basic parameters
 - 1-week transition probabilities, $\pi_{i,j}$
- Data on 1-week transitions
 - directly inform basic parameters, $\pi_{i,j}$
- Data on K-step transitions,
 - indirectly inform basic parameters:

$$\pi_{1,j}^1 = \pi_{1,j}$$

$$\pi_{1,j}^K = \sum_{i=1}^I \pi_{1,i}^{(K-1)} \pi_{i,j} \quad K = 2, \dots$$

Study 1: 1-week transition data

$r_{i,j}$	STW	UTW	Hex	Pex	TF	Row Total, n_i
STW	210	60	0	1	1	272
UTW	88	641	0	4	13	746
Hex	0	0	0	0	0	0
Pex	1	0	0	0	1	2
TF	0	0	0	0	81	81

$$r_{i,1:5} \sim \text{Multinomial}(\boldsymbol{\pi}_{i,1:5}, n_i)$$

Dirichlet priors

Study 2: K-week transition data

One row of:

$r_{1,j}^K$	STW	UTW	Hex	Pex	TF	Row Total, n_i^K
K=2 STW	110	64	1	1	5	181
K=3 STW	92	80	0	1	8	181
K=4 STW	80	88	1	1	11	181
...	181

$$r_{1,1:5}^K \sim \text{Multinomial}(\pi_{1,1:5}^K, n_1^K)$$

- K-step transition probabilities defined recursively:

$$\pi_{1,j}^1 = \pi_{1,j}$$

$$\pi_{1,j}^K = \sum_{i=1}^I \pi_{1,i}^{(K-1)} \pi_{i,j} \quad K = 2, \dots$$

WinBUGS Code (1)

```
model{
for (i in 1:4){      #There are 4 non-absorbing health states
  r[i,1:5] ~ dmulti(pi[i,1:5],n[i]) #1-step likelihood

  for (j in 1:5) {   #Dirichlet prior for 1-week probs.
    pi[i, j] <- delta[i, j] / sum(delta[i,])
    delta[i, j] ~ dgamma(1, 1)
  }
}

rK[1:5]~dmulti(piK[1:5],nK) #K-step likelihood
```

WinBUGS Code (2)

#To obtain K-year probabilities, piK

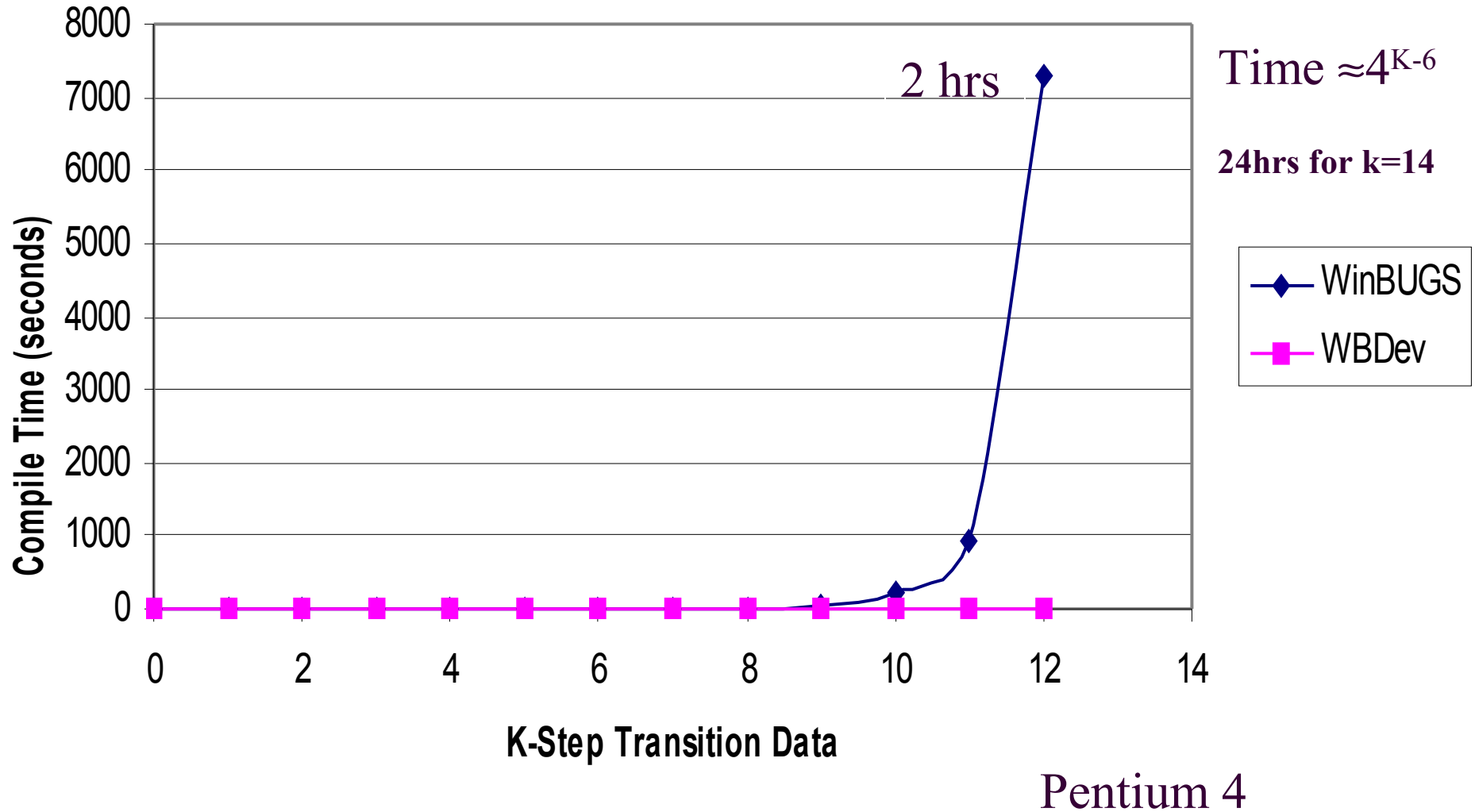
```
for (i in 1:4){ prob[i,1]<- 1*equals(i,1) }    #Start in STW  
  for (t in 2:(K+1)){                          #Run the model for K cycles  
    for (i in 1:4){                              # Use inprod function  
      prob[i,t]<- inprod(prob[1:4,t-1], pi[1:4,i])  
    }  
    prob[5,t]<-1-sum(prob[1:4,t]) #probs must sum to 1  
  }  
  for (i in 1:5){ piK[i]<-prob[i,(K+1)]}  
}
```

WBDev Function

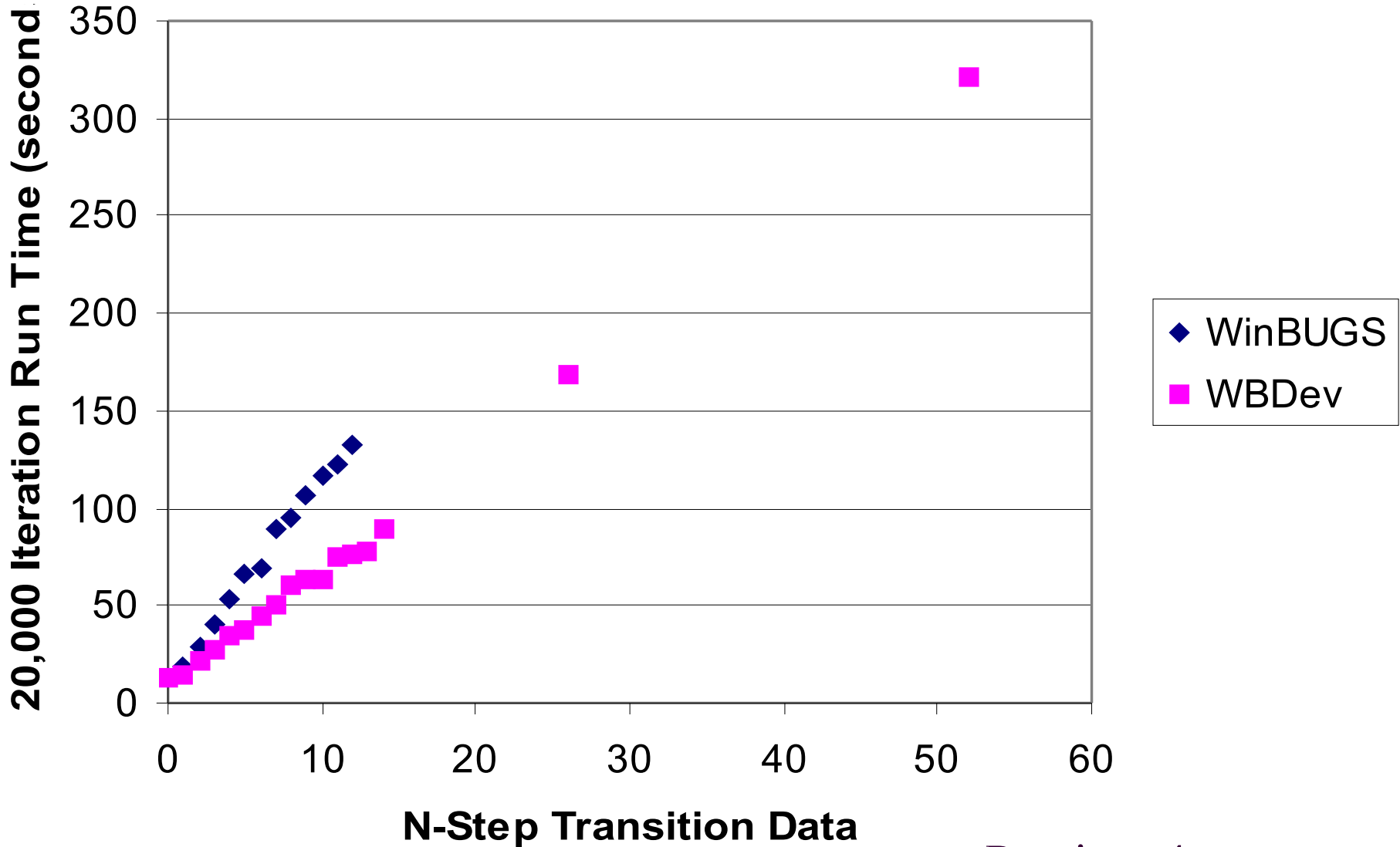
```
#To obtain K-week probabilities, piK  
#Replace WinBUGS code with WBDev function  
#asthma5.inprod
```

```
piK[1:5]<-  
asthma5.inprod(pi[1,1:5],pi[2,1:5],pi[3,1:5],pi[4,1:5],K)  
}
```

Results: Compile Time



Results: Run Time



More Complex Models

- Asthma Meta-Analysis / HIV Infection model
- Compile time will make such a synthesis impractical, unless we use WBDev
- Quite common for studies to have K-step transition data
 - where some individuals miss an appointment
 - Different studies use different follow-up
- Further complications if working with transition rates ... WBDiff

Early Onset Group B Streptococcus (EOGBS)

- Infection acquired during delivery, leading to disease in 4.5 / 10,000 newborns in first week of life
- High risk of meningitis, 15% fatality given EOGBS
- Screening mothers during pregnancy, treatment with antibiotics routine in USA
- Should we be screening in UK ?

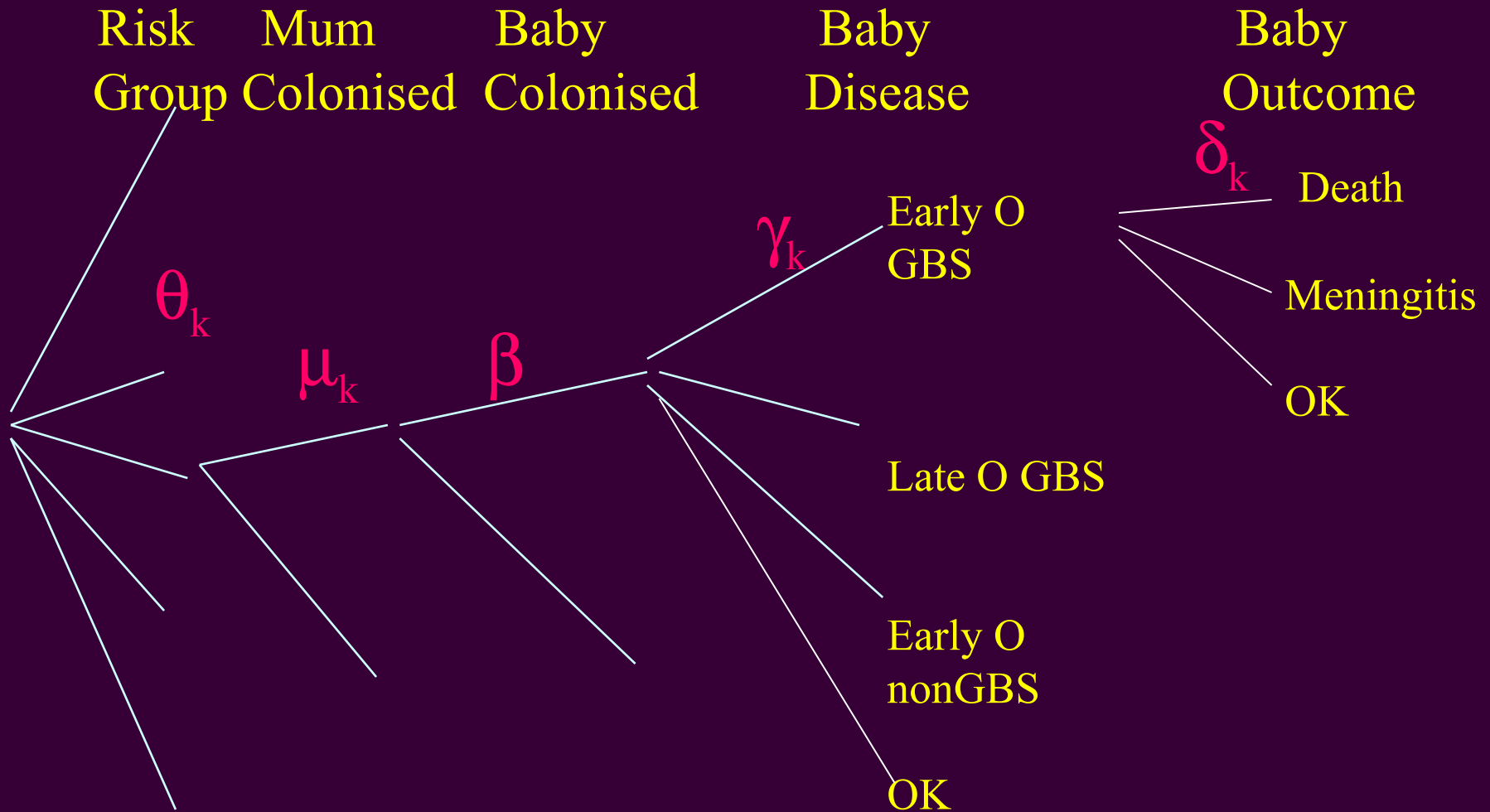
6 Pre-term Maternal Risk Groups

1. Pre-term Planned LSCS (Caesarean)
2. Pre-term Previous GBS baby
3. Pre-term GBS bacteriuria/positive swab
4. Pre-term pyrexia (fever)
5. Pre-term pre-labour ROM \geq 2hrs
6. Pre-term ROM $<$ 2hrs, pre-labour on or after labour onset

6 Term Maternal Risk Groups

1. Term Planned LSCS (Caesarean)
2. Term Previous GBS baby
3. Term GBS bacteriuria/positive swab
4. Term pyrexia (fever)
5. Term ROM > 18hrs
6. No risk factors (Term)

Group –B Strep decision tree



- Ideally, prospective study
- In practice have many retrospective studies (given baby disease)
- This is the simplified version (Mum non-colonised, baby outcomes ...)

Studies on maternal Risk Groups, θ_k

$$\theta_k = \begin{cases} \tau p(k | pre-term) & k = 1, \dots, 6 \\ (1 - \tau) p(k | term) & k = 7, \dots, 12 \end{cases}$$

$$\tau = p(pre-term)$$

1. No. of pre-term babies: England & Wales
Hospital Episodes Statistics (HES) data
 $rt \sim Binomial(\tau, nt)$
3. SMMIS data on combinations of risk
groups conditional on term/pre-term

Studies on maternal Risk Groups, θ_k

1. Log-odds previous GBS baby (Halliday et al):
 $\text{logit}(\theta_2 + \theta_8)$
4. Log-odds GBS bacteriuria and/or previous positive swab (Expert opinion): $\text{logit}(\theta_3 + \theta_9)$
6. Log-odds pre-term given GBS bacteriuria (McKenzie et al) : $\text{logit}(\theta_3) - \text{logit}(\theta_9)$

Studies on Maternal Colonisation Given Risk Group, μ_k

1. Average maternal colonisation rates
(Gray): $\Sigma \theta_k \mu_k$
- Prior for log-odds of colonisation in term relative to pre-term (McDonald et al):
 $\text{logit}(\mu_{k+6}) - \text{logit}(\mu_k)$

Studies on Neonatal Colonisation Given Maternal Colonisation

1. Prior for baby colonisation given maternal colonisation (Hammoud et al): β

Studies on Disease Status Given Baby Colonisation, γ_k

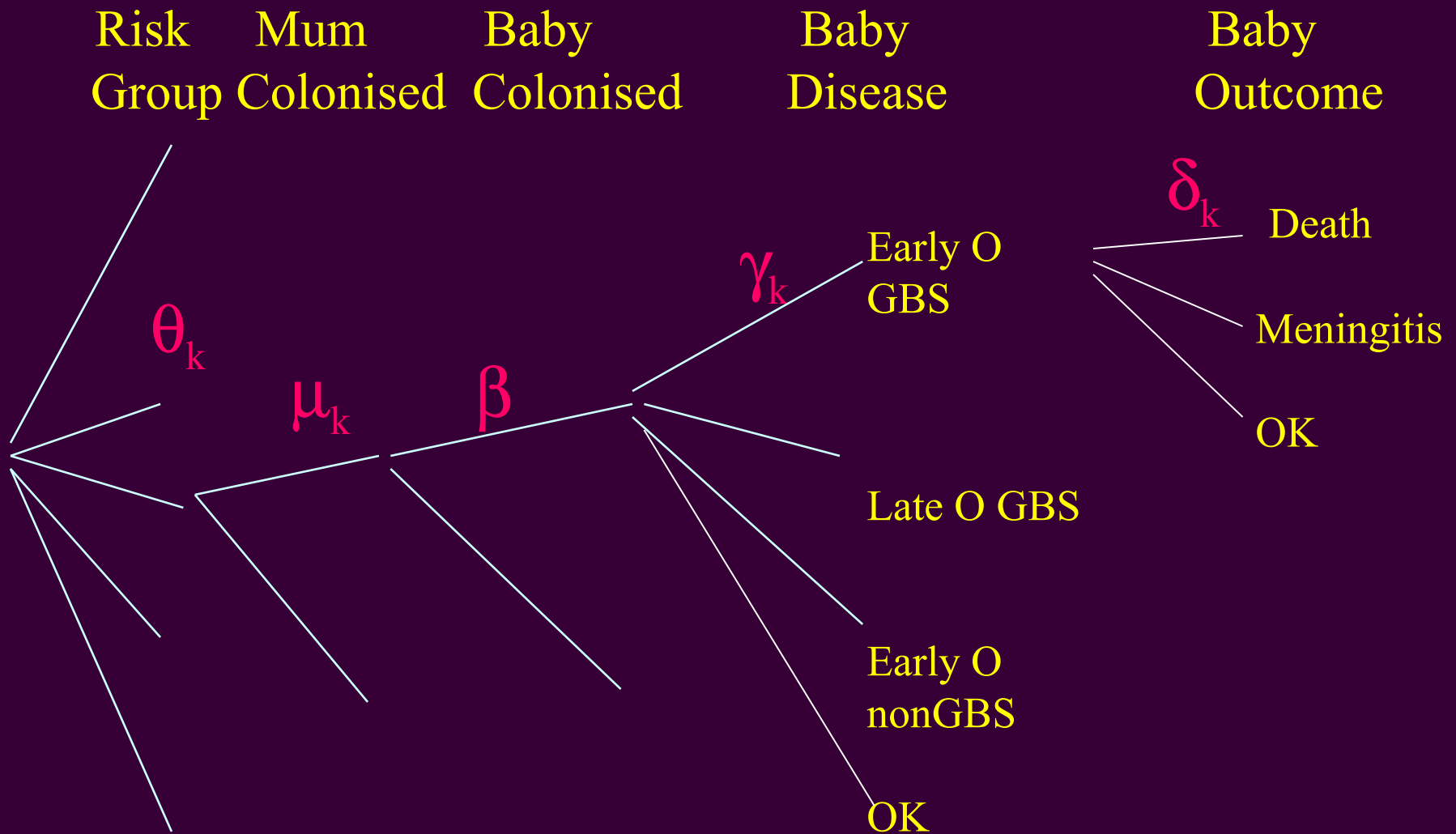
2. Total EOGBS in population (Heath & Oddie) :

$$\sum_{k=1}^{12} \theta_k \mu_k \beta \gamma_k$$

- Proportion of EOGBS in risk group k (Heath & Oddie) : $\lambda_k = \theta_k \mu_k \beta \gamma_k / \sum_{k=1}^{12} \theta_k \mu_k \beta \gamma_k$

9. Priors for γ_k based on data from control arm RCTs

Group –B Strep decision tree



Studies on Disease Status Given Baby Colonisation, γ_k

1. Proportion of EOGBS that are pre-term (Pooled all UK): $\sum_{k=1}^6 \lambda_k$
3. Log-odds of previous GBS babies in all EOGBS (Beardsall et al) : $\text{logit}(\lambda_2 + \lambda_8)$
5. Log-odds of pyrexia in all EOGBS (Pooled all UK) : $\text{logit}(\lambda_4 + \lambda_{10})$
7. Log-odds of any risk factors in all EOGBS (Pooled all UK) : $\text{logit}(\lambda_{12})$

Studies on Disease Status Given Baby Colonisation, γ_k

1. EOGBS divided into maternal risk groups:
Multinomial with probabilities (Oddie) :

$$\lambda_1, \dots, \lambda_{12}$$

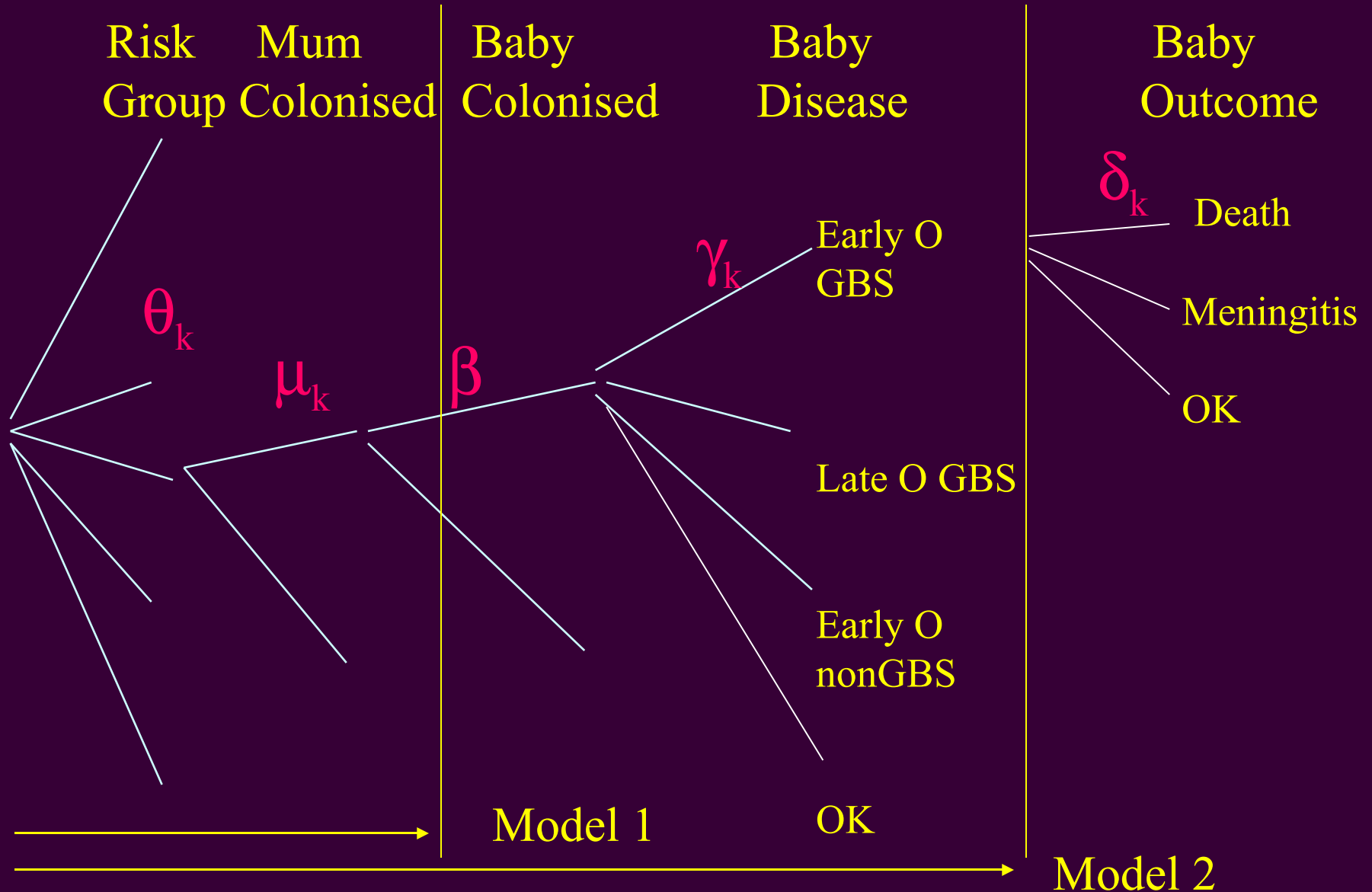
5. Average probability of EOGBS given
baby colonised (Baker et al) :

$$\frac{\sum_{k=1}^{12} \theta_k \mu_k \gamma_k}{\sum_{k=1}^{12} \theta_k \mu_k}$$

Modelling Issues

- All priors vague or evidence-based
- Although many data sources, the data is sparse and the model is only just identifiable

Group –B Strep decision tree



Results (60,000 samples)

Model	WinBUGS	WBDev	% Reduction
Model 2: Maternal Risk Group + Maternal Colonisation	151secs (2.5 mins)	65secs (1.1mins)	57%
Model 3: + Baby Colonisation & Disease Status	880secs (14.7mins)	268secs (4.5 mins)	70%

Further Data

- There is more data on mortality, meningitis, treatment effects (IV antibiotics)...
- Will be even slower ...
- Again, this type of problem is quite typical
- Retrospective studies OFTEN give data on these kinds of structures

Summary

- Given two examples of the types of model we want to be able to fit in WinBUGS
- Both examples presented are actually very common
- Need to find quick/efficient methods to find posterior summaries for such models
- WBDev seems to provide a solution to the problems we encountered with these two examples

Web Resources

- MRC HSRC Evidence Synthesis Programme

http://www.hsrc.ac.uk/Current_research/research_programmes/mpes.htm

- WBDDev & WBDiff

http://homepages.tesco.net/~creeping_death/

Further Data

- Death|EOGBS, δ_k
- Total EOGBS deaths in population,
 $\sum_k \theta_k \mu_k \beta \gamma_k \delta_k$
- Information on IV antibiotics:
 - Some trials report
 - Prob (baby colonisation | mum colonisation)
 - Prob (EOGBS | baby colonisation)
 - Others
 - Prob (EOGBS | mum colonisation)
- Will be even slower ...

EOGBS synthesis issues

- Difficult decisions on which data to include:
 - UK data only on maternal colonisation as transmission mechanisms vary between countries
 - USA/ Europe data useful to inform risk factors for
 - baby colonisation | mum colonisation,
 - EOGBS | baby colonisation,
 - death | EOGBS
- Sparse data, many assumptions ... model checking difficult