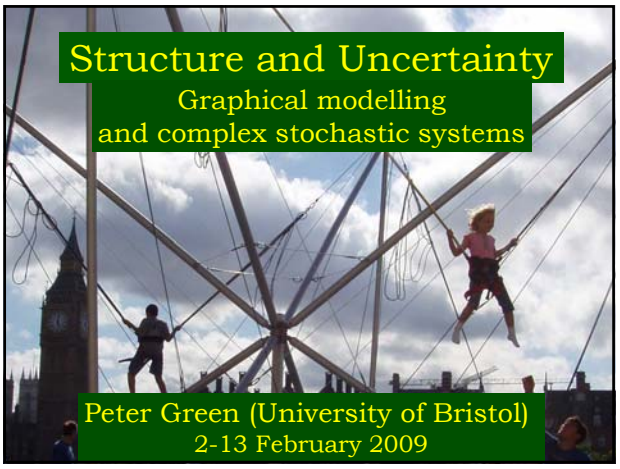


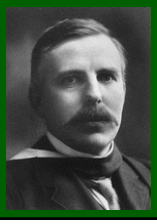
Structure and Uncertainty

Graphical modelling
and complex stochastic systems

Peter Green (University of Bristol)
2-13 February 2009

What has statistics to say about science and technology?

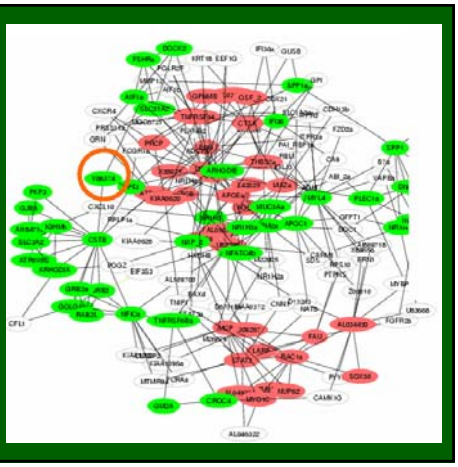
Statistics and science



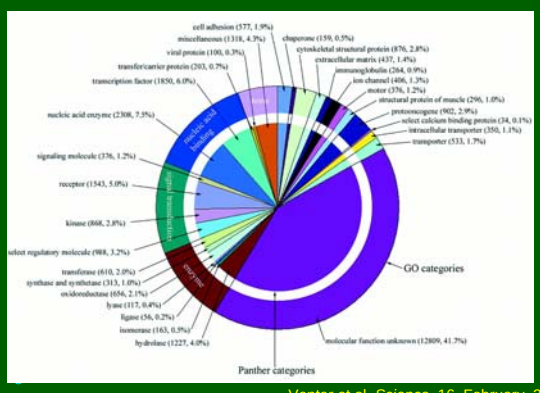
Ernest Rutherford (1871-1937)

What has statistics to say about the complexity of modern science?

Gene networks

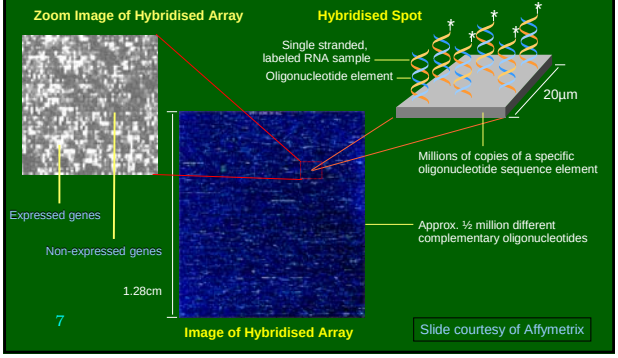


Functional categories of genes in the human genome



Venter et al, *Science*, 16 February, 2001

Gene expression using Affymetrix microarrays



Slide courtesy of Affymetrix

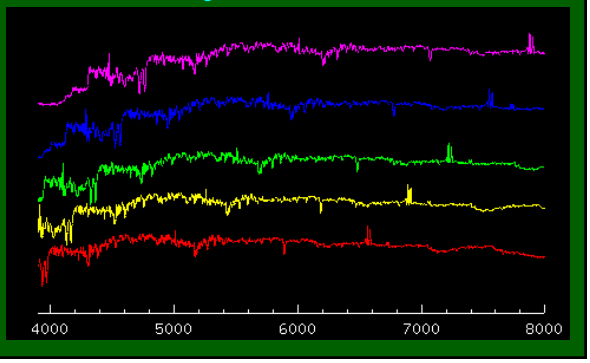
7

8

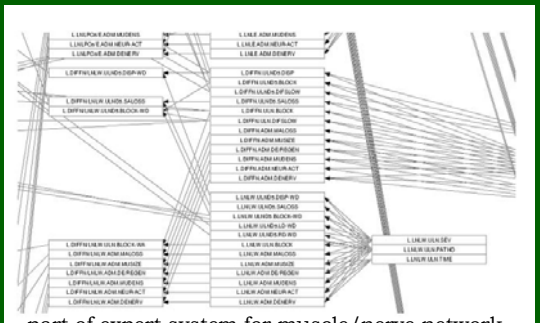
Velocity of recession determines 'colour' through redshift effect

9

Astronomy: redshifts



Probabilistic expert systems



part of expert system for muscle/nerve network

Complex stochastic systems

Problems in these areas – and many others - have been successfully addressed in a modern statistical framework of structured stochastic modelling

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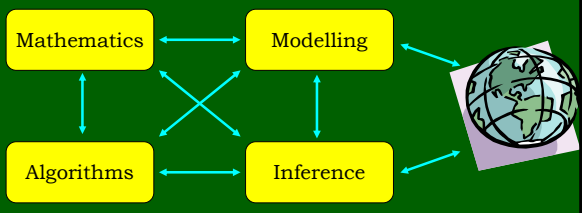
Graphical modelling



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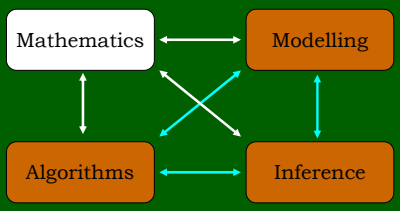
1. Mathematics



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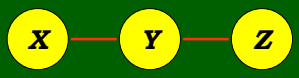
Conditional independence

- X and Z are conditionally independent given Y if, knowing Y, discovering Z tells you nothing more about X: $p(X \mid Y,Z) = p(X \mid Y)$
- $X \perp Z \mid Y$



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Coin-tossing

- You take a coin from your pocket, and toss it 10 times and get 10 heads
- What is the chance that the next toss gives head?

Now suppose there are two coins in your pocket – a 80-20 coin and a 20-80 coin – what is the chance now?

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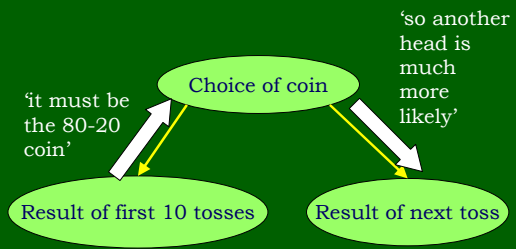
Coin-tossing



(conditionally independent given coin)
(the odds on a head are now 3.999986 to 1)

17

Conditional independence

as seen in data on perinatal mortality vs. ante-natal care....

Clinic	Ante	Survived	Died	% died
A	less	176	3	1.7
	more	293	4	1.3
B	less	197	17	7.9
	more	23	2	8.0

Does survival depend on ante-natal care?

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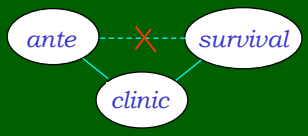
.... what if you know the clinic?

Conditional independence



survival and *clinic* are dependent

and *ante* and *clinic* are dependent

but *survival* and *ante* are CI given *clinic*

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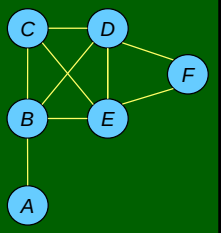
Graphical models

Use ideas from graph theory to

- represent structure of a joint probability distribution
- by encoding conditional independencies



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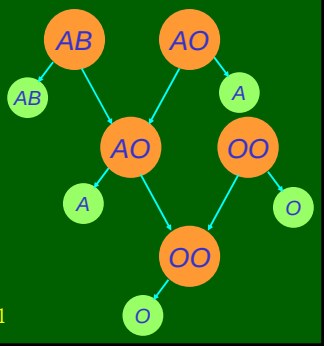
Mendelian inheritance - a natural structured model

Mendel



Where does the graph come from?

- Genetics
  - pedigree (family connections)
- Physical and biological systems
  - supposed causal effects
- Contingency tables
  - hypothesis tests on data
- Gaussian case
  - graph determined by non-zeroes in inverse variance matrix (i.e. non-zero partial correlations)

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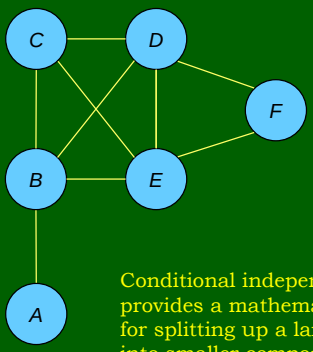

Conditional independence provides a mathematical basis for splitting up a large system into smaller components

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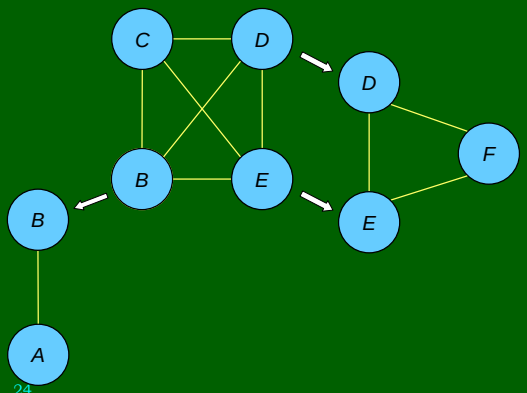

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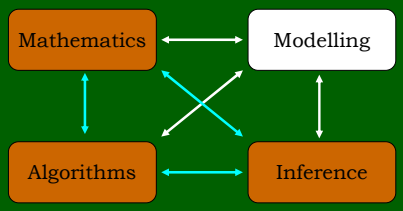
2. Modelling



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Structured systems

A framework for building models, especially probabilistic models, for empirical data

Key idea -

- understand complex system
- through global model
- built from small pieces
  - comprehensible
  - each with only a few variables
  - modular

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Modular structure

Basis for

- understanding the real system
- capturing important characteristics statistically
- defining appropriate methods
- computation
- inference and interpretation

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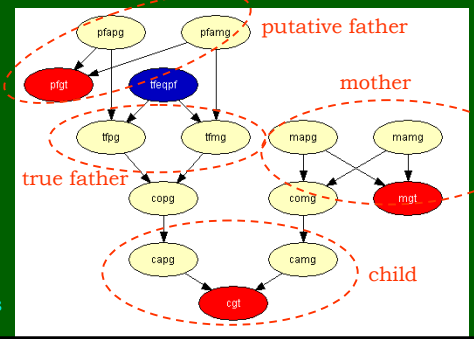
Building a model, for genetic testing of paternity using DNA probes



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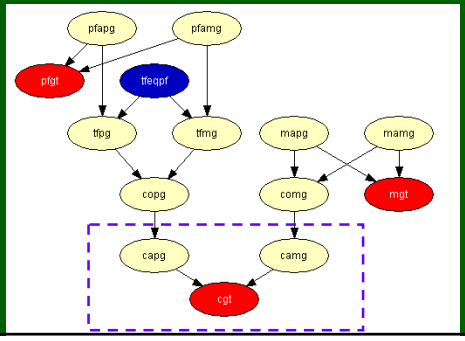
Building a model, for genetic testing of paternity



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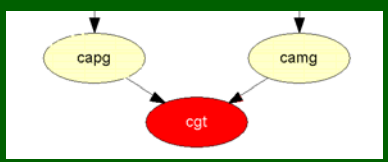
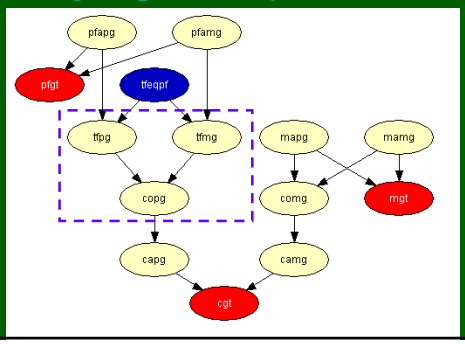
… genes determine genotype



e.g. if child's paternal gene is '10' and maternal gene is '12', then its genotype is '10-12'

30

Building a model, for genetic testing of paternity



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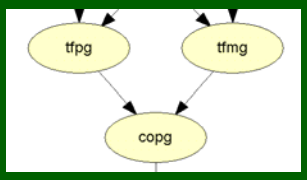
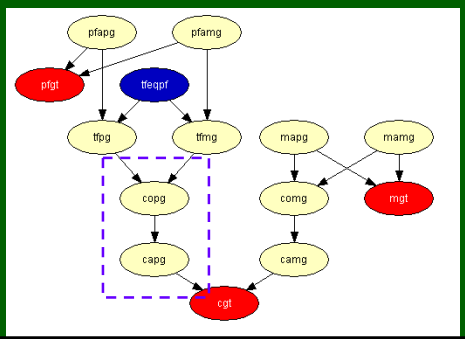
… Mendel's law



the gene that the child gets from the father is equally likely to have come from the father's father or mother

32

Building a model, for genetic testing of paternity



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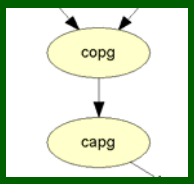
… with mutation



there is a small probability of a gene mutating

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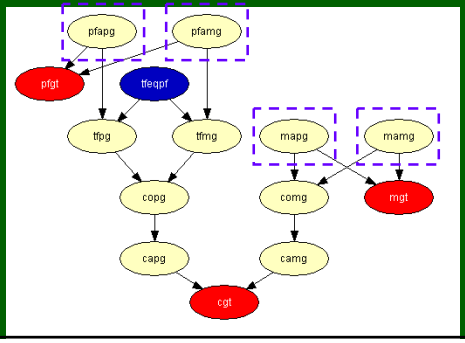
Building a model, for genetic testing of paternity



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… using population data

we need gene frequencies relevant to assumed population for 'founder' nodes

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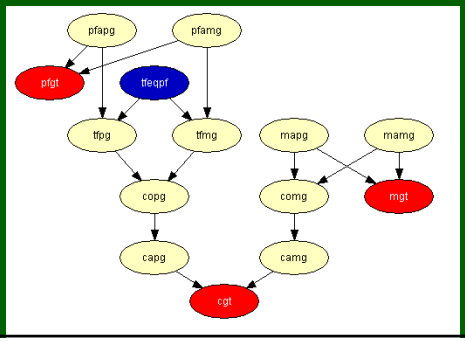
Building a model, for genetic testing of paternity



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Building a model, for genetic testing of paternity

- Having established conditional probabilities within each of these local models….
- We can insert 'evidence' (data) and draw probabilistic inferences…

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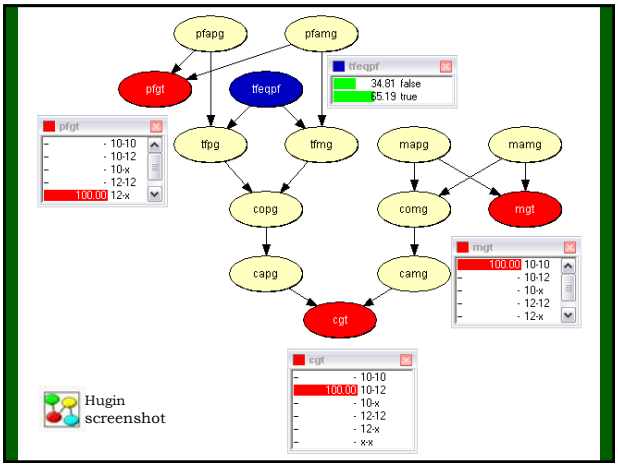

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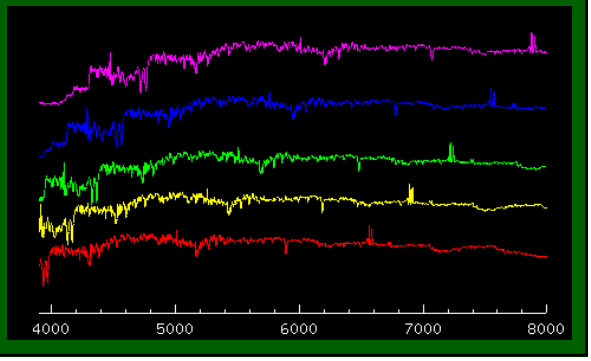
Photometric redshifts



Photometric redshifts

$$x_{ij} = a_j + b_i + M\left(\sum_{\ell=1}^{4} w_{i\ell} M^{-1}\{\psi_{\ell j}(z_i)\}\right) + \varepsilon_{ij}$$

$$\psi_{\ell j}(z) = \int h_j((1+z)u)\phi_\ell(u)du$$

$M(\cdot) = -2.5\log_{10}(\cdot)$
magnitude $= M$(flux)

42

Photometric redshifts

$$x_{ij} = a_j + b_i + M\left(\sum_{\ell=1}^{4} w_{i\ell} M^{-1}\{\psi_{\ell j}(z_i)\}\right) + \varepsilon_{ij}$$

Multiplicative model (on flux scale), involving an unknown mixture of templates

$$M(\cdot) = -2.5\log_{10}(\cdot)$$

magnitude $= M$(flux)

43

Photometric redshifts

redshift

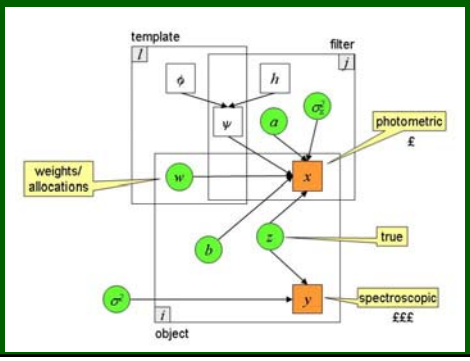
filter response

template

$$\psi_{\ell j}(z) = \int h_j((1+z)u)\phi_\ell(u)du$$

44

Photometric redshifts



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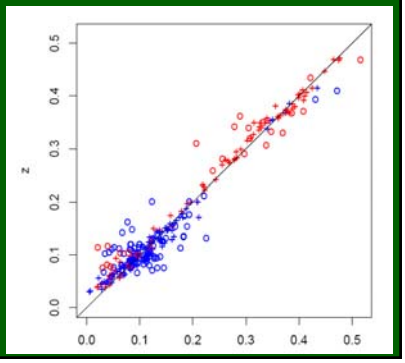
Photometric redshifts

good agreement with 'gold-standard' spectrographic measurement



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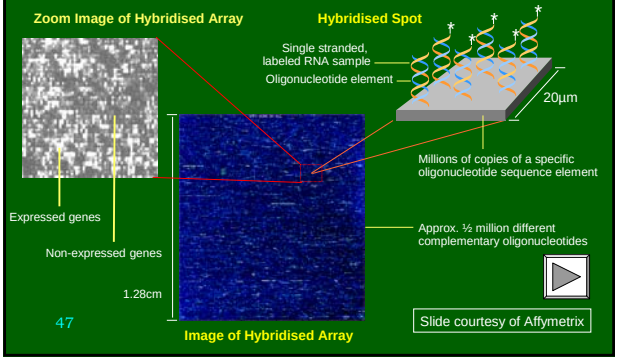
Gene expression using Affymetrix microarrays



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Variation and uncertainty

Gene expression data (e.g. Affymetrix™) is the result of multiple sources of variability

- condition/treatment
- biological
- array manufacture
- imaging
- technical
- within/between array variation
- gene-specific variability

Structured statistical modelling allows considering all uncertainty at once

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Single array model: motivation

(Hein, Richardson, Causton, Ambler & G, 2004)

Key observations:		Conclusions:
PMs and MMs both increase with spike-in concentration (MMs slower than PMs)	→	MMs bind fraction of signal
Spread of PMs increase with level	→	Multiplicative (and additive) error; transformation needed
Considerable variability in PM (and MM) response within a probe set	→	Varying reliability in gene expression estimation for different genes
Probe effects approximately additive on log-scale	→	Estimate gene expression measure from PMs and MMs on log scale

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BGX single array model

$PM_{gj} \sim N(S_{gj} + H_{gj}, \tau^2)$

$MM_{gj} \sim N(\Phi S_{gj} + H_{gj}, \tau^2)$

Background noise, additive

fraction

signal

Non-specific hybridisation

$\log(S_{gj}+1) \sim TN(\mu_g, \xi_g^2)$ $j=1,\ldots,J$

$\log(H_{gj}+1) \sim TN(\lambda, \eta^2)$

Gene expression index (BGX): θ_g=median(TN (μ_g, ξ_g^2))
"Pools" information over probes j=1,…,J

Gene specific error terms: exchangeable

Array-wide distribution

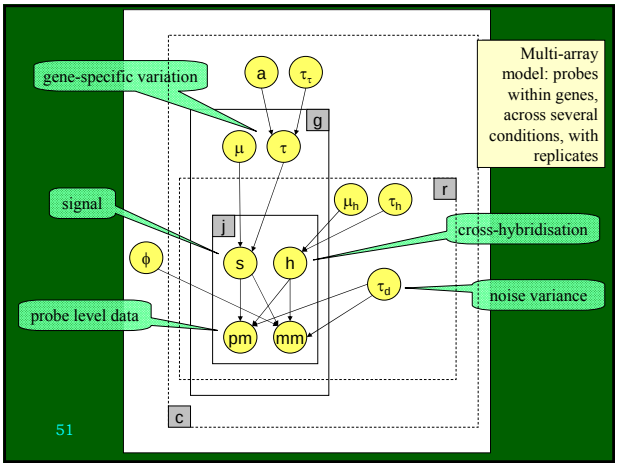
"Empirical Bayes"

$\log(\xi_g^2) \sim N(a, b^2)$

Priors: "vague" $\tau^2 \sim \Gamma(10^{-3}, 10^{-3})$ $\Phi \sim B(1,1)$, $\mu_g \sim U(0,15)$ $\eta^2 \sim \Gamma(10^{-3}, 10^{-3})$, $\lambda \sim N(0,10^3)$

g=1,…,G (thousands), j=1,…,J (11-20)

50



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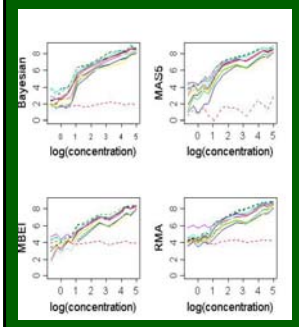
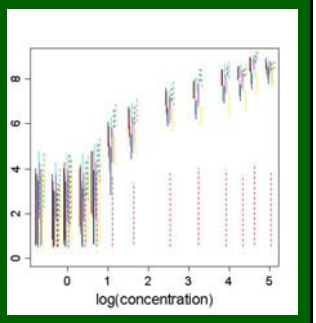
Single array model performance:
11 genes spiked in at 13 (increasing) concentrations

Hein, Richardson, Causton, Ambler & G, 2004

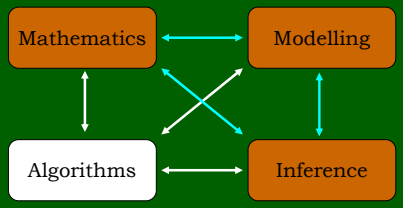




Indication of good resolution at low concentrations and probably reduced bias

Unlike competitors, method provides confidence intervals

3. Algorithms



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Algorithms for probability and likelihood calculations

Exploiting graphical structure:

- Markov chain Monte Carlo
- Probability propagation (Bayes nets)
- Expectation-Maximisation
- Variational (mean-field) methods

Graph representation used in user interface, data structures and in controlling computation

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Markov chain Monte Carlo

- Subgroups of one or more variables updated randomly,
  - maintaining detailed balance with respect to target distribution
- Ensemble converges to equilibrium = target distribution (= Bayesian posterior, e.g.)

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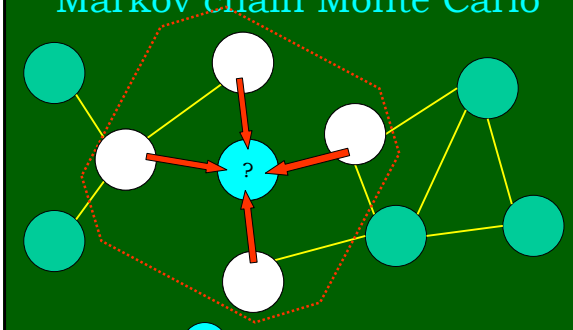
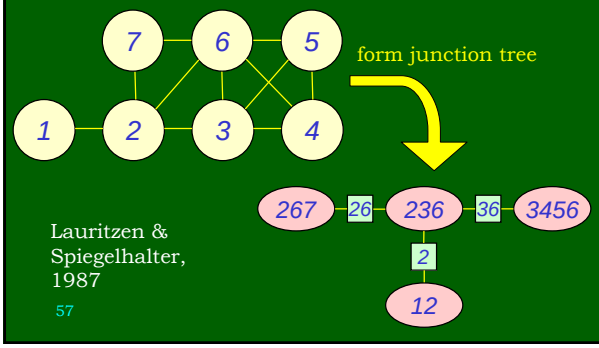
Markov chain Monte Carlo



56 Updating ? - need only look at neighbours

Probability propagation



Lauritzen & Spiegelhalter, 1987

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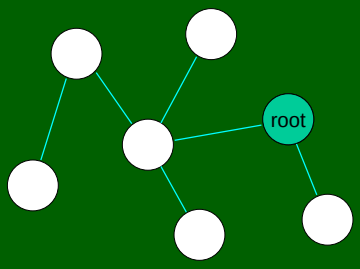
Message passing in junction tree



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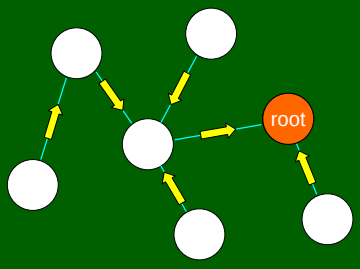
Message passing in junction tree - collect



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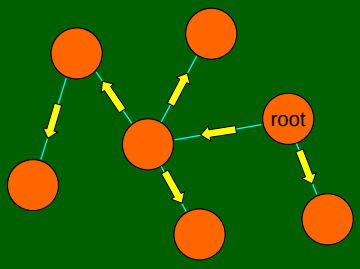
Message passing in junction tree - distribute



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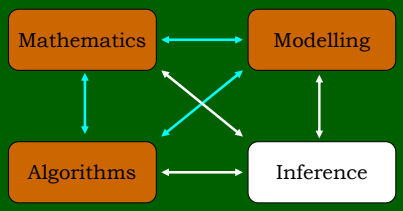
4. Inference



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Bayesian

62

or non-Bayesian

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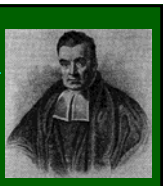
Bayesian paradigm in structured modelling



- 'borrowing strength'
- automatically integrates out all sources of uncertainty
- properly accounting for variability at all levels
- including, in principle, uncertainty in model itself
- avoids over-optimistic claims of certainty

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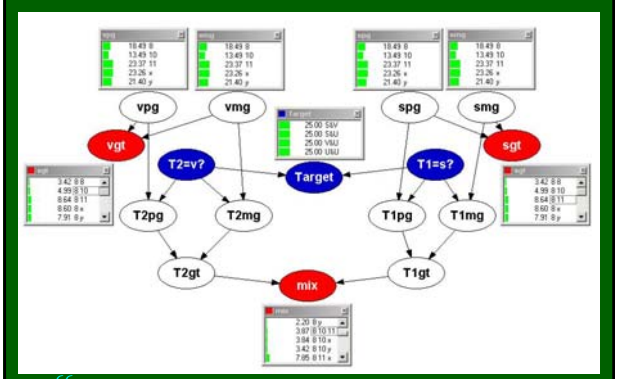
Bayesian structured modelling

- 'borrowing strength'
- automatically integrates out all sources of uncertainty
- … for example in forensic statistics with DNA probe data…..

65



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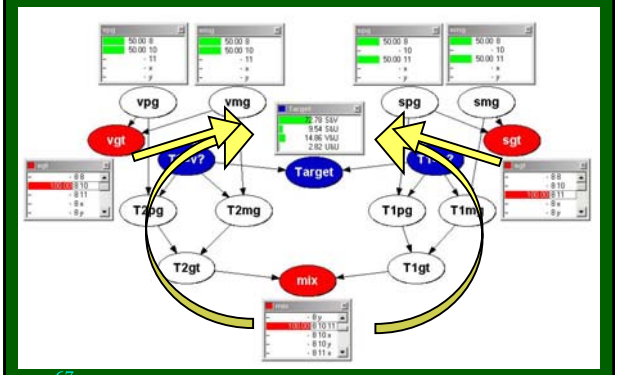

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Bayesian structured modelling

- 'borrowing strength'
- automatically integrates out all sources of uncertainty
- … for example in hidden Markov models for disease mapping

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John Snow's 1855 map of cholera cases

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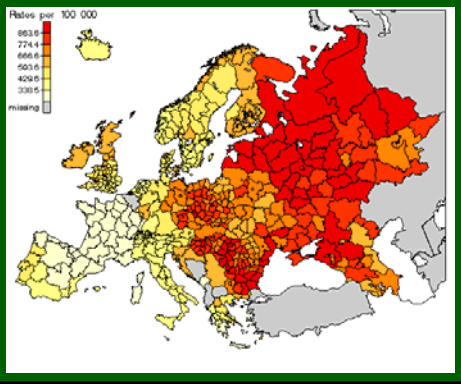
Mortality for diseases of the circulatory system in males in 1990/1991



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Disease mapping

- Observe counts y_i of cases of rare, non-infectious disease in regions i
- Standard model:

$$y_i \sim \text{Poisson}(\lambda_i E_i)$$

- where E_i are adjusted populations at risk
- Relative risks λ_i vary due to unmeasured risk factors, assumed spatially correlated
- Use space as surrogate to separate signal and noise

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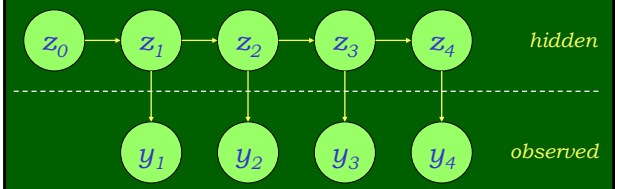
Hidden Markov models

e.g. Hidden Markov chain



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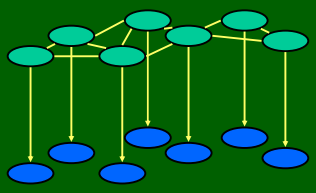
Hidden Markov random fields



Unobserved dependent field

Observed conditionally-independent (e.g. discrete) field

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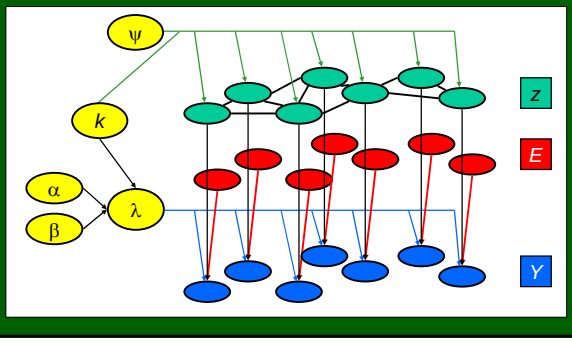
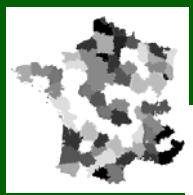
Hierarchical mixture model for disease mapping – a hidden MRF

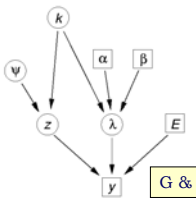


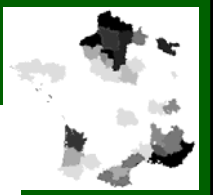
Mapping of rare diseases
using Hidden Markov model



Larynx cancer in females in France, 1986-1993 (standardised ratios)

75





Posterior probability of excess risk

G & Richardson, 2002

Bayesian structured modelling

- 'borrowing strength'
- automatically integrates out all sources of uncertainty
- … for example in modelling complex biomedical systems like ion channels…..

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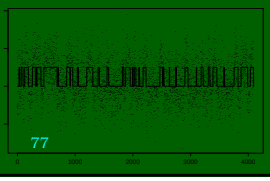
Ion channel model

Hodgson and Green, Proc Roy Soc Lond A, 1999



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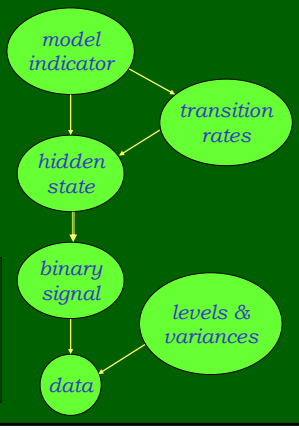

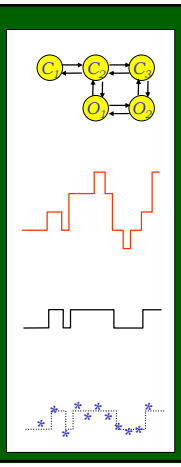

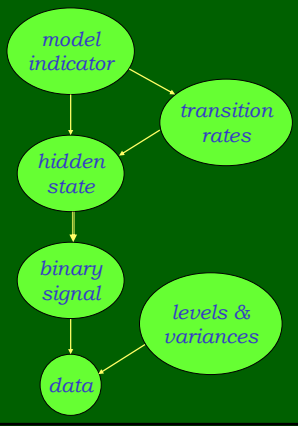

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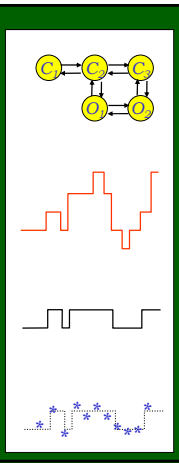

Unknown physiological states of channel, unknown connections

Continuous time Markov chain on this graph, with unknown transition rates

Only open/closed status of states is relevant to observation

We observe only in discrete time, with highly correlated noise

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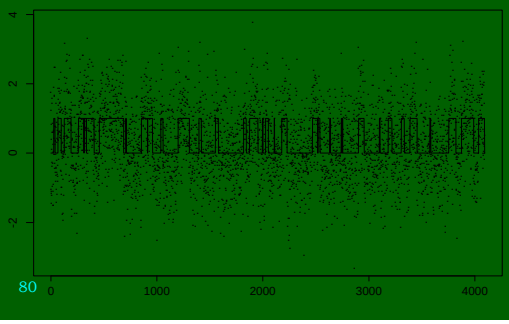
Truth and simulated data



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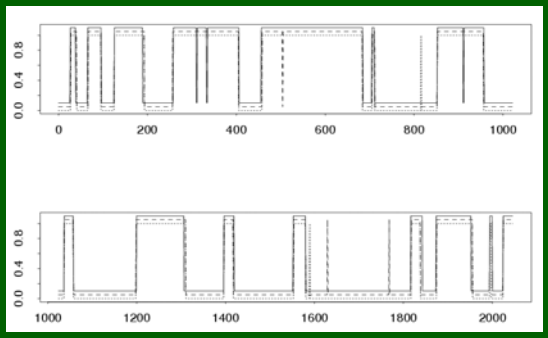
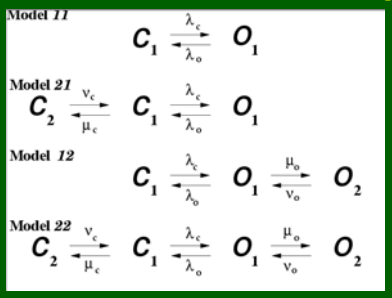
Truth and 2 restorations



Ion channel model choice

posterior probabilities



.405

.119

.369

.107

82

Structured systems' success stories include...

- Genomics & bioinformatics
  - DNA & protein sequencing, gene mapping, evolutionary genetics
- Spatial statistics
  - image analysis, environmetrics, geographical epidemiology, ecology
- Temporal problems
  - longitudinal data, financial time series, signal processing

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Structured systems' challenges include...

- Very large/high-dimensional data sets
  - genomics, telecommunications, commercial data-mining...

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Summary

Structured stochastic modelling (the 'HSSS' approach) provides a powerful and flexible approach to the challenges of complex statistical problems

- Applicable in many domains
- Allows exploiting scientific knowledge
- Built on rigorous mathematics
- Principled inferential methods

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http://www.stats.bris.ac.uk/~peter

P.J.Green@bristol.ac.uk

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