# Bioinformatics 2 - Lecture 4

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# Sequences

- Many data types are ordered, i.e. you can naturally say what is before and what is after
- Chief example, data with a time series structure
- Other key biological example, sequences (order given by polarity of the molecules)
- Any other examples right in front of your eyes?

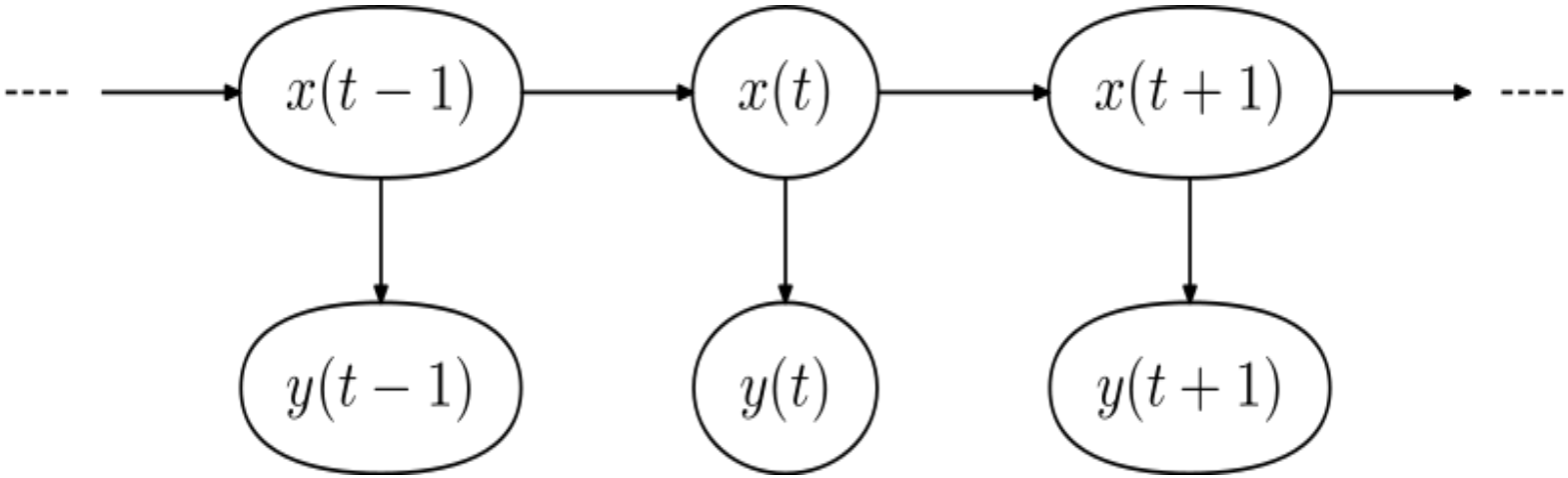
# Latent variables in sequential data

- Sometimes what we observe is not what we are interested in
- For example, in a medical application, one could think of a person being either healthy (H), diseased (D) or recovering (R)
- What we measure are (related) quantities such as the temperature, blood pressure, $O_2$ concentration in blood, ...
- The job of the doctor is to *infer* the latent state from the measurements

# Latent variables in sequential data

- In a transcriptomic experiment, we can measure mRNA abundance at different time points after a stimulus
- What we may be really interested in is the concentration of active *transcription factor* proteins, which may give a more direct insight in how the cells respond to the stimulus
- Again, we are interested in reconstructing a latent variable from observations; this time the latent variables are continuous (concentrations)

# Network representation of latent variables




- We represent the latent states as a sequence of random variables; each of them depends *only* on the previous one
- The observations depend only on the corresponding state

# States and parameters

- We are interested in the posterior distribution of the states $x_{1:T}$ given the observations $y_{1:T}$ (subscript $1:T$ denotes the collection of variables from 1 to $T$)
- Notice that we only have one observation per time point
- In the independent observations case, this would not be enough
- We also have parameters which we assume known: these are in the known probabilities

$$\pi = p(x(1)) \quad T_{x(t-1),x(t)} = p(x(t)|x(t-1)) \quad O_{x,y} = p(y(t)|x(t)$$

- We assume parameters to be time-independent

# The single time marginals

- The joint posterior over the states is, by the rules of probability, proportional to the joint probability of observations and states

$$p\left(x_{1:T}|y_{1:T}\right) \propto p\left(x_{1:T}, y_{1:T}\right)$$

- An object of central importance is the *single time marginal* for the latent variable at time $t$
- This is obtained by marginalising the latent variables at all other time points; by the proportionality above

$$p\left(x(t)|y_{1:T}\right) \propto p\left(x(t), y_{1:T}\right)$$

# Networks and factorisations

- By using the product rule of probability, we can rewrite the joint probability of states and observations as

$$\begin{aligned} & p\left(x_{1:T}, y_{1:T}\right) = \\ & = p\left(y_{t+1:T} | x_{1:T}, y_{1:t}\right) p\left(x_{1:T}, y_{1:t}\right) \end{aligned} \tag{1}$$

- Recall that networks encode *conditional independence* relations; in particular, areas of the network which are not directly connected are independent of each other *given* the nodes in between.

# Some conditional independencies

- By inspection of the network representation of the model (slide 4), we see that

$$p\left(y_{t+1:T}|x_{1:T}, y_{1:t}\right) = p\left(y_{t+1:T}|x_{t+1:T}\right) \tag{2}$$

- Also $x_{t+1:T}$ are conditionally independent of $y_{1:t}$ given $x_t$, so that

$$\begin{aligned} &p\left(x_{1:T}, y_{1:t}\right) = p\left(x_{t+1:T}|x_{1:t}, y_{1:t}\right) p\left(x_{1:t}, y_{1:t}\right) = \\ &p\left(x_{t+1:T}|x_t\right) p\left(x_{1:t}, y_{1:t}\right) \end{aligned} \tag{3}$$

# Factorisations and messages

- Putting equations (2,3) into (1), we get

$$p\left(x_{1:T}, y_{1:T}\right) = p\left(y_{t+1:T}, x_{t+1:T} | x_t\right) p\left(x_{1:t}, y_{1:t}\right)$$

- Marginalising $x_{1:t-1}$ and $x_{t+1:T}$ we get the following *fundamental factorisation* of the single time marginal

$$\begin{aligned} p\left(x(t)|y_{1:T}\right) &\propto \alpha(x(t))\beta(x(t)) = \\ &= p\left(x(t)|y_{1:t}\right) p\left(y_{t+1:T}|x(t)\right) \end{aligned} \tag{4}$$

- The single time marginal at time $t$ is the product of the posterior estimate given all the data *up to that point*, times the likelihood of future observations given the state at $t$

# Aside for Informaticians and like minded people

- The factorisation in equation (4) is an example of *message passing*
- $\alpha(x(t))$ is a message propagated forwards from the previous observations (forward message or filtered process)
- $\beta(x(t))$ is a message propagated backwards from future observations (backward message)
- Message passing algorithms allow exact inference in tree structured graphical models (why?) and approximate inference in more complicated models

# Filtering: computing the forward message

- *Initialisation*:

$$\alpha(1) \propto p\left(y(1), x(1)\right) = \pi O_{x(1),y(1)}$$

- *Recursion*:

$$\begin{aligned}\alpha(t) \propto & p\left(x(t), y_{1:t}\right) = \sum_{x(t-1)} p\left(x(t), x(t-1), y_{1:t}\right) = \\ & = \sum_{x(t-1)} p\left(y(t)|x(t)\right) p\left(x(t)|x(t-1)\right) p\left(x(t-1)|y_{1:t-1}\right) = \\ & = \sum_{x(t-1)} O_{x(t),y(t)} T_{x(t-1),x(t)} \alpha(x(t-1))\end{aligned}$$

  where I used the conditional independences of the network to go from line 1 to 2

- If $x(t)$ is a continuous, replace the sum with an integral

# Computing the backward message

- *Initialisation*: $\beta(x(T)) = 1$ (why?)
- *Backward recursion*:

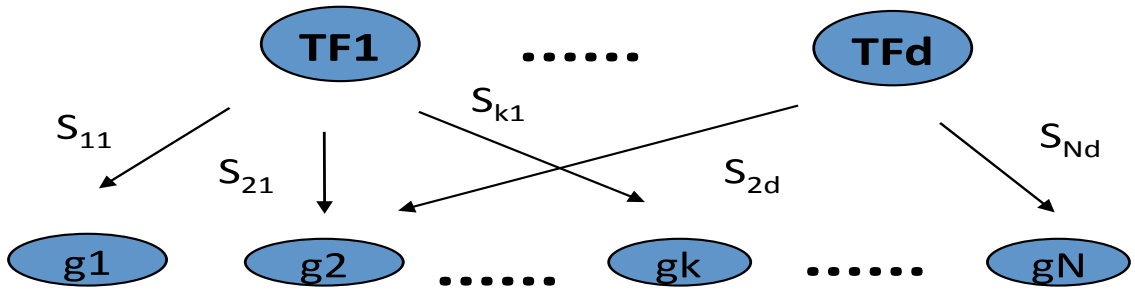
$$\beta(x(t-1)) = p\left(y_{t:T}|x(t-1)\right) = \sum_{x(t)} p\left(y_{t:T}, x(t)|x(t-1)\right) =$$

$$= \sum_{x(t)} p\left(y_{t+1:T}|y(t), x(t), x(t-1)\right) p\left(y(t)x(t)|x(t-1)\right) =$$

$$= \sum_{x(t)} \beta(x(t)) p\left(y(t)|x(t)\right) p\left(x(t)|x(t-1)\right)$$

- Once again, if $x$ is continuous replace sum with integral

# Biological problem




- In some organisms, some of the wiring of the network is known
- Simplest possible model, log-linear model of gene expression

$$g_i(t) = \sum_j S_{ij} X_{ij} TF_j(t) + \epsilon$$

where $X$ is a binary matrix encoding the network and $\epsilon \simeq \mathcal{N}(0, \sigma^2)$ is an error term

# Inference in the model of transcriptional regulation

- The simple model of regulation states that gene expression levels are a weighted linear combination of TF levels
- Usually, we do not know the TF (protein) levels, so we treat this as a latent variable problem
- To incorporate dynamics, we assume the TF levels at time $t$ to depend on the levels at time $t-1$, and gene expression measurements to be conditionally independent given TF levels
- Both TF and gene expression levels are assumed to be Gaussian; Linear Dynamical System (LDS)

# LDS priors and jargon

- The time evolution of the hidden states is given by a Gaussian random walk

$$x(t+1) = Ax(t) + w(t) \rightarrow p\left(x(t+1)|x(t)\right) = \mathcal{N}\left(x(t), \Sigma_w\right) \tag{5}$$

- The term $w \sim \mathcal{N}(0, \Sigma_w)$ is they *system noise* term; the matrix $A$ is sometimes called the *gain* matrix.
- Observations are related to states using another linear Gaussian model

$$y(t) = Bx(t) + \epsilon(t) \rightarrow p\left(y(t)|x(t)\right) = \mathcal{N}\left(Bx(t), \Sigma_\epsilon\right) \tag{6}$$

where $\epsilon \sim \mathcal{N}(0, \Sigma_\epsilon)$ is the *observation noise* and $B$ is the *observation* matrix

# Inference for LDS

- Since both noises are Gaussian and all equations are linear, all the messages will be Gaussian
- This simplifies the inference as we do not need to compute normalisation constants
- For example, the forward message is computed as

$$\alpha(x(t)) = \mathcal{N}(x(t)|\mu_t, \Sigma_t) =$$
$$\int dx(t-1)\alpha(x(t-1))\mathcal{N}(x(t)|Ax(t-1), \Sigma_w)\mathcal{N}(y(t)|Bx(t), \Sigma_\epsilon)$$

- *Exercise*: calculate the forward message

# Biological motivations

- In many cases, we observe intrinsically discrete variables (e.g. DNA bases)
- Also, we are interested in intrinsically discrete latent states (e.g. is this fragment of DNA a gene or not?)
- These situations often arise when dealing with problems in genomics and functional genomics
- We will give three examples, and show some details on how to deal with one of these

# How to find genes

- The outcome of a sequencing experiment is the sequence of a region of the genome
- Which parts of the sequence gets transcribed into mRNA?
- Possible solution: sequence the mRNA (laborious)
- Alternatively, use the *codon effect*: genic DNA is not uniformly distributed since triplets of basis code for specific amino-acids
- Thus, the sequence of a gene will look different from the sequence of a not gene region

# CpG islands

- In the genome, a G nucleotide preceded by a C nucleotide is rare (strong tendency to be methylated and mutate into T)
- In some regions related to promoters of genes, methylation is inhibited so many more C followed by G (CpG)
- These functional regions are called CpG islands and they are characterized by a different nucleotide distribution

# ChIP-on-chip data

- Technology to measure binding of transcription factors to DNA
- Observe an intensity signal (optical)
- Want to infer whether a certain intensity associated with a certain fragment of DNA implies binding or not
- More in Ian Simpson's guest lecture

# Hidden Markov Models jargon

- When the latent states can only assume a finite number of discrete values, we have a Hidden Markov Model (HMMs)
- HMMs have a long history in speech recognition and signal processing and they have their own terminology
- The conditional probabilities $p\left(x(t+1)|x(t)\right)$ are called *transition probabilities*. They are collected in a matrix

$$T_{ij} = p\left(x(t+1) = i|x(t) = j\right)$$

- The conditional probabilities $p\left(y(t)|x(t)\right)$ are called *emission probabilities*. If the observed variables are also discrete, we can collect the emission probabilities in another matrix

$$O_{ij} = p\left(y(t) = i|x(t) = j\right)$$

# Inference in HMM

- The forward and backward messages are simply computed as matrix multiplications involving emission and transition matrices
- The forward message is

$$\alpha(t) \propto \sum_{x(t-1)} O_{x(t),y(t)} T_{x(t-1),x(t)} \alpha(x(t-1))$$

- The backward message is

$$\beta(t-1) = \sum_{x(t)} \beta(x(t)) p\left(y(t)|x(t)\right) p\left(x(t)|x(t-1)\right)$$

# HMM for CpG islands

- We construct latent variables with eight states representing bases in normal DNA and CpG regions, (A,C,G,T,$\bar{\mathrm{A}}$,$\bar{\mathrm{C}}$,$\bar{\mathrm{G}}$,$\bar{\mathrm{T}}$)
- The $8 \times 8$ transition matrix will have very low entry for $T_{C,G}$ and higher entry for $T_{\bar{\mathrm{C}},\bar{\mathrm{G}}}$
- The emission matrix is just $O_{x,x} = 1 = O_{x,\bar{x}}$ with all other entries zero, indicating that the observation is just the nucleotide without the CpG/ normal label
- The specific entries in the transition matrix will be determined from annotated databases