Bone Journal Club
Math Modeling for Bone-Cell Dynamics

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Overview

Why?

- It is an attempt to introduce theoretical foundations to biological processes.
- It can also explain also some of the paradoxical observations.
- Based on "mechanistic" assumptions, models can produce useful predictions.
- Once a model is "calibrated", it can accommodate extensions based on new biological findings.

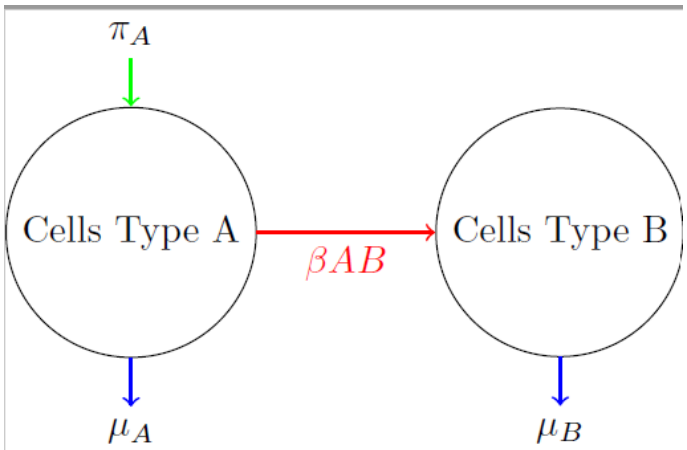
Compartmental Models

The so-called **Compartmental Models** try to describe the dynamics of cell interactions among two or more well-characterized cell types. Some basic implicit assumptions about cell populations

- The evolution of the population is described by rates (i.e., instant changes in population numbers).
- Cells are indistinguishable among the same type (A and B below).
- A and B represent abundance of the given type.

Compartmental Models (cont)

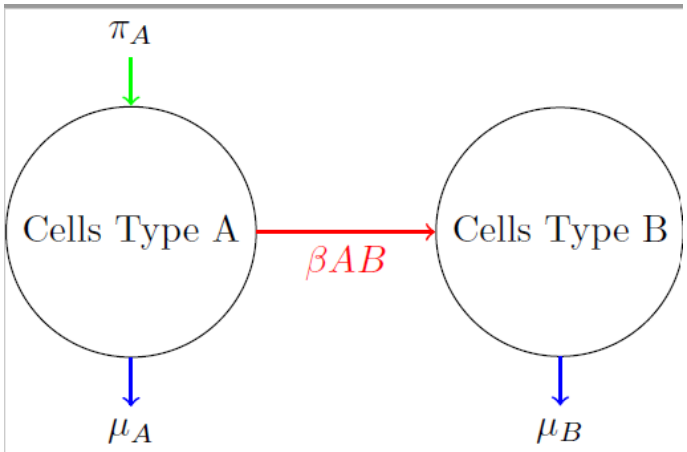
- Cells are entering (some progenitor cell) into the A compartment at a certain rate π_A.
- Cells leave the compartment (cell death) at the rate μ_A and μ_B, respectively.
- Cells evolve from Type A into Type B at a rate proportional to their abundance at a constant rate β.



Compartmental Model Math

The translation of this interaction is translated in the following system of (ordinary) differential equations

$$\begin{aligned} A' &= \pi_A - \beta AB - \mu_A A \\ B' &= \beta AB - \mu_B B \end{aligned} \tag{1}$$



"Solving" the equations

For the above system, we can calculate the "steady state(s)". This means the point(s) that the trajectories will end up reaching (after potentially some very long time) or they are getting away from.

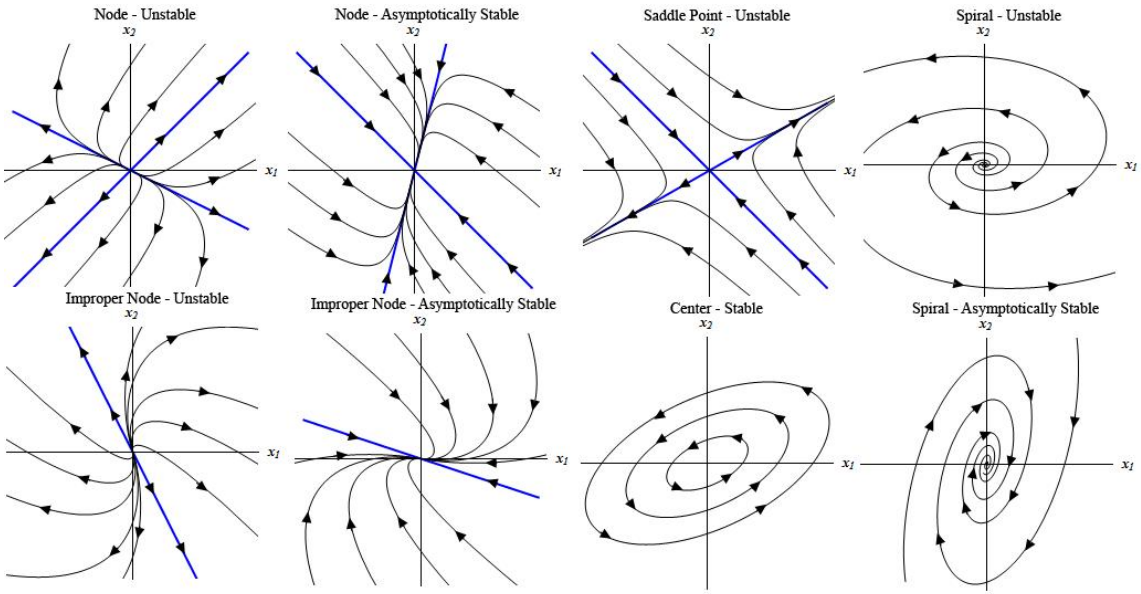
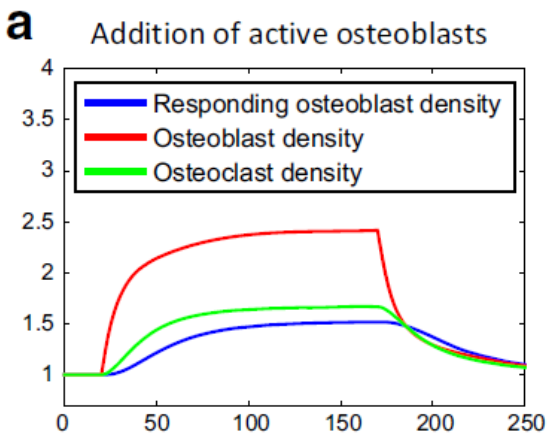


Figure: dynamical systems

"Solving" the equations (cont)

In general, it is relatively hard to calculate those steady states and determine (locally) their behavior (attractor or repelor) (Mathematical issue)
Instead, we solve the equations "numerically". Meaning, we write code to simulated the trajectories (e.g., Matlab) for a given set of parameters (π_A, β, etc.)



In Silico Simulations

A great deal of time is spent calculating the parameters from a given established system

- Using other literature sources
- Making simulations based on newly produced data

The ultimate goal is to produce a tuned *in silico* system based on equations that mimic fundamental biological concepts. Then, we can explore scenarios and test biological hypothesis.

Today's paper

Bulletin of Mathematical Biology (2019) 81:3575–3622
https://doi.org/10.1007/s11538-018-0533-0

Society for Mathematical Biology

SPECIAL ISSUE: MATHEMATICS TO SUPPORT DRUG DISCOVERY AND DEVELOPMENT

CrossMark

Dynamics of Bone Cell Interactions and Differential Responses to PTH and Antibody-Based Therapies

Vincent Lemaire[1,2] · David R. Cox[1]

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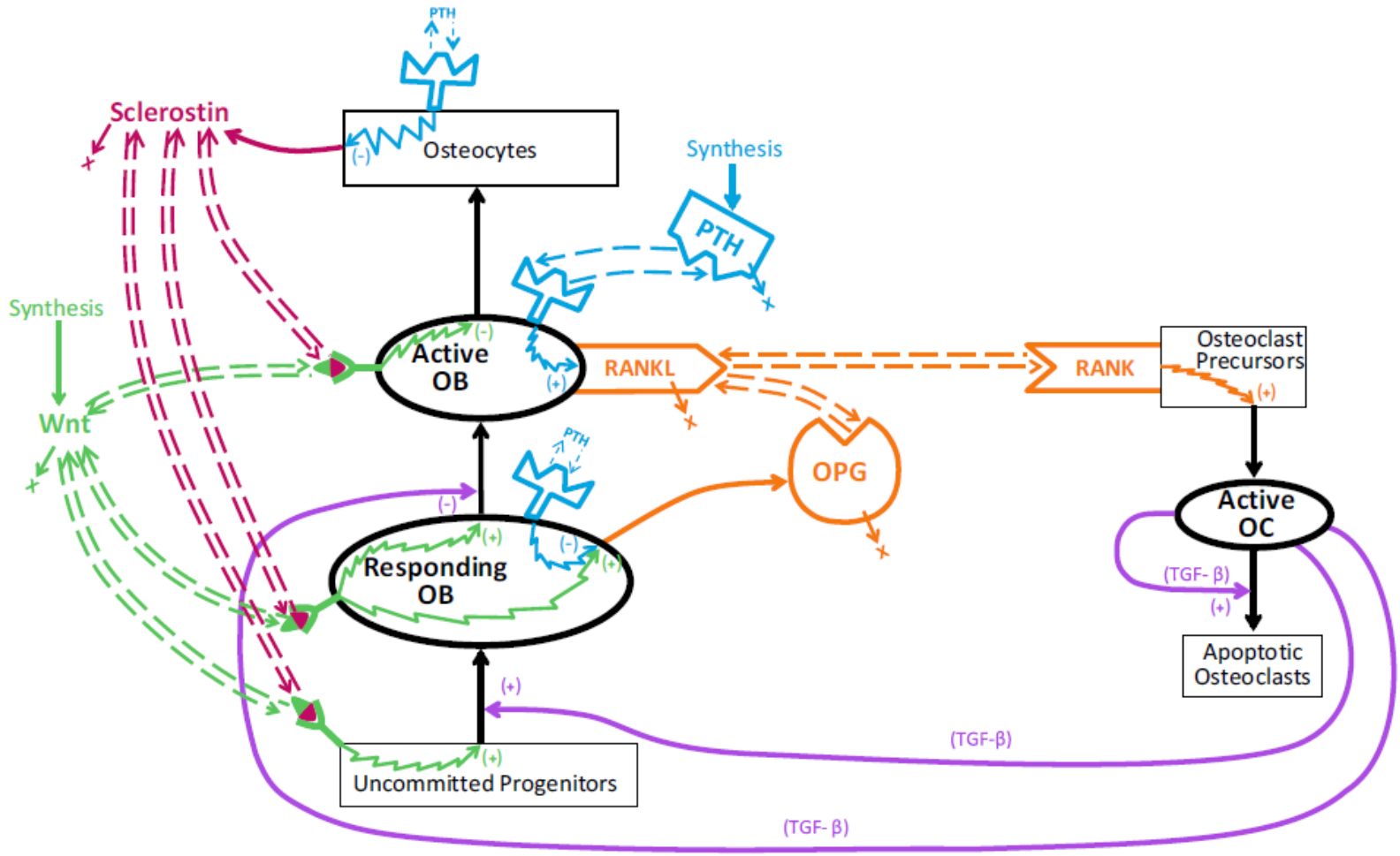
Picture First



Cell Compartment Equations

$$
\begin{aligned}
R' &= D_R \pi_C \pi_W - D_B \frac{\pi_W}{\pi_C} R \\
B' &= D_B \frac{\pi_W}{\pi_C} R - \frac{k_e^B}{\pi_W} B \\
C' &= D_C \pi_L - k_e^C \pi_C C
\end{aligned}
\tag{2}
$$

According to the model D_R, D_B and D_C are constant differentiation rates, k_e^B, and k_e^C are constant elimination rates.

Ligands Models

The modeling follows the enzymatic theory of Michaelis-Menten. In brief, if we have a substrate S reacting with an enzyme E to form a complex SE can be modeled as

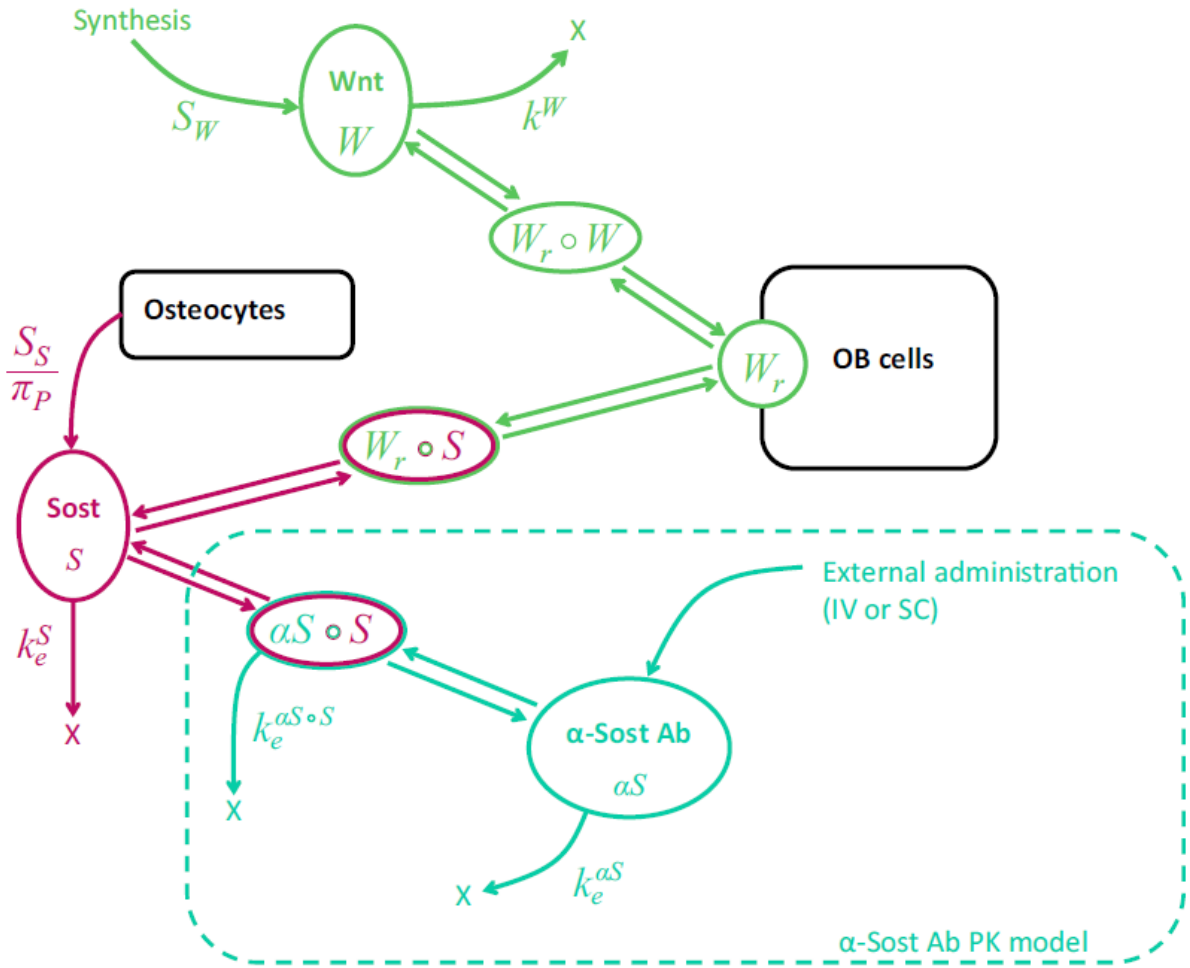
$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} S \circ E$$

$$\frac{dS \circ E}{dt} = k_1 S \cdot E - k_{-1} S \circ E \tag{3}$$

When the text refers that equations are considered at "steady state" it means that

$$k_1 S \cdot E = k_{-1} S \circ E$$

Ligand Models (cont)



Binding to LPR5/6

The attachment of Wnt to the receptor W_r is taken at the steady state. The equations for binding of Wnt receptor and sclerostin are

$$\begin{aligned} \frac{dW_r \circ S}{dt} &= k_9 S \cdot W_r - k_{10} W_r \circ S \\ \frac{d\alpha S \circ S}{dt} &= k_{13} S \cdot \alpha S - k_{14} \alpha S \circ S - k_e^{\alpha S \circ S} \alpha S \circ S \end{aligned} \tag{4}$$

The second equation represents the presence of an antibody for Sost

Parameter Estimation

Table 2 These are the parameters of the bone model which were determined by optimization (fitting parameters)

Symbol	Unit	Value	Description
D_R	pM/day	1.28×10^{-4}	Differentiation rate of osteoblast progenitors into responding osteoblasts [see Eq. (1)]
f_0	None	3.39×10^{-2}	Minimal TGF-β receptor occupancy [see Eq. (2)]
C_{50}	pM	1.25×10^{-6}	Osteoclast density to achieve half TGF-β receptor occupancy [see Eq. (2)]
D_B	day^{-1}	3.47	Differentiation rate of responding osteoblasts into active osteoblasts [see Eq. (1)]
k_e^B	day^{-1}	1.21×10^{-3}	Rate of elimination/death of active osteoblasts [see Eq. (1)]
D_C	pM/day	7.12×10^{-3}	Differentiation rate of osteoclast progenitors into active osteoclasts [see Eq. (1)]
k_e^C	day^{-1}	6.46×10^{-2}	Rate of elimination/death of active osteoclasts [see Eq. (1)]
K_D^O	pM	4.76×10^{-6}	Mixed parameter representing a typical density of OPG-producing cells [see Eq. (36)]
K_{max}^L	pmol/pmol of cells	4644.6	Maximum carrying capacity of cell-bound RANKL by osteoblasts [see Eq. (28)]
k_3	$\text{pM}^{-1}\ \text{day}^{-1}$	0.368	RANK-RANKL association rate [Eq. (25)]
k_4	day^{-1}	65.64	RANK-RANKL dissociation rate [Eq. (25)]
K_D^P	None	20.17	Mixed parameter related to unbound PTH receptors in basal condition [see Eq. (24)]
K	pM	0.10	RANK density [see Eq. (26)]
K_D^S	None	14.95	Mixed parameter related to unbound sclerostin molecules in basal condition [see Eq. (19)]
K_D^W	None	3.70	Mixed parameter related to unbound Wnt molecules in basal condition [see Eq. (19)]

Journal Club Format

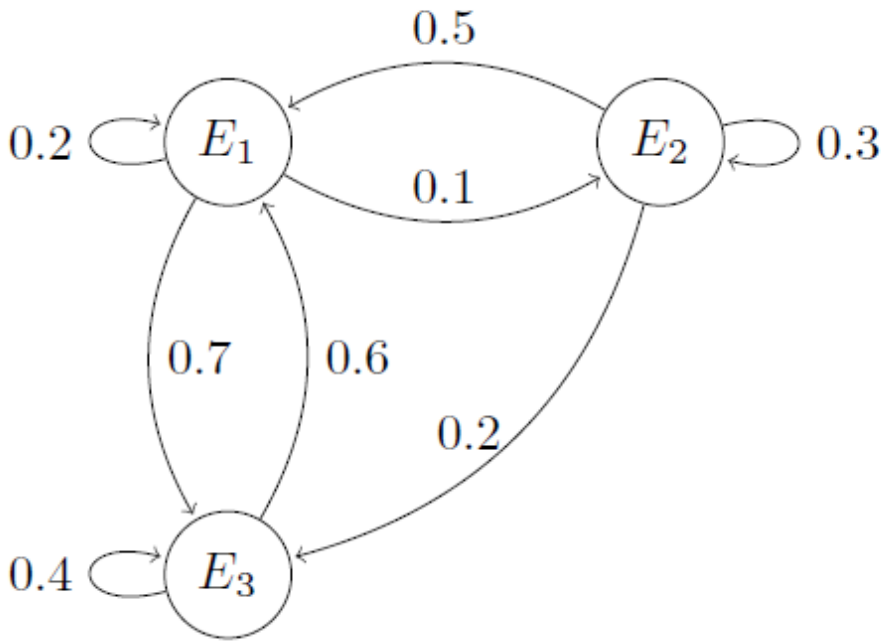
This is a new format for Journal Club

- We will explore more carefully the methodology.
- Most of the papers are going to require "heavy" tools from computer sciences, statistics and mathematics.
- It will be a transition time to understand each other (be patient)
- The dynamical nature of brain activity will make it very challenging to hold on to a single model.
- Complexity vs. Explainability is an implicit trade-off.
- The ultimate goal is to use and expand "acceptable" methodologies into new and more "appropriate" ones. Yes, this means **coding** (R, Python, MatLab).

Hidden Markov Models

The implementation of Hidden Markov models dates back in the late 60's by Leonard Baum and collaborators. It is still an active area of research.

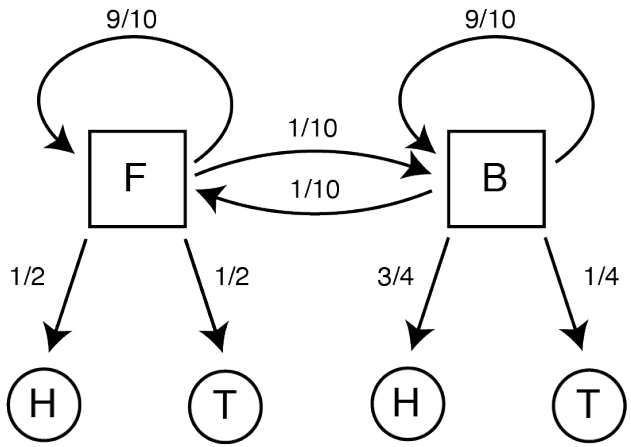
What is a Markov chain?



Hidden Markov Chains

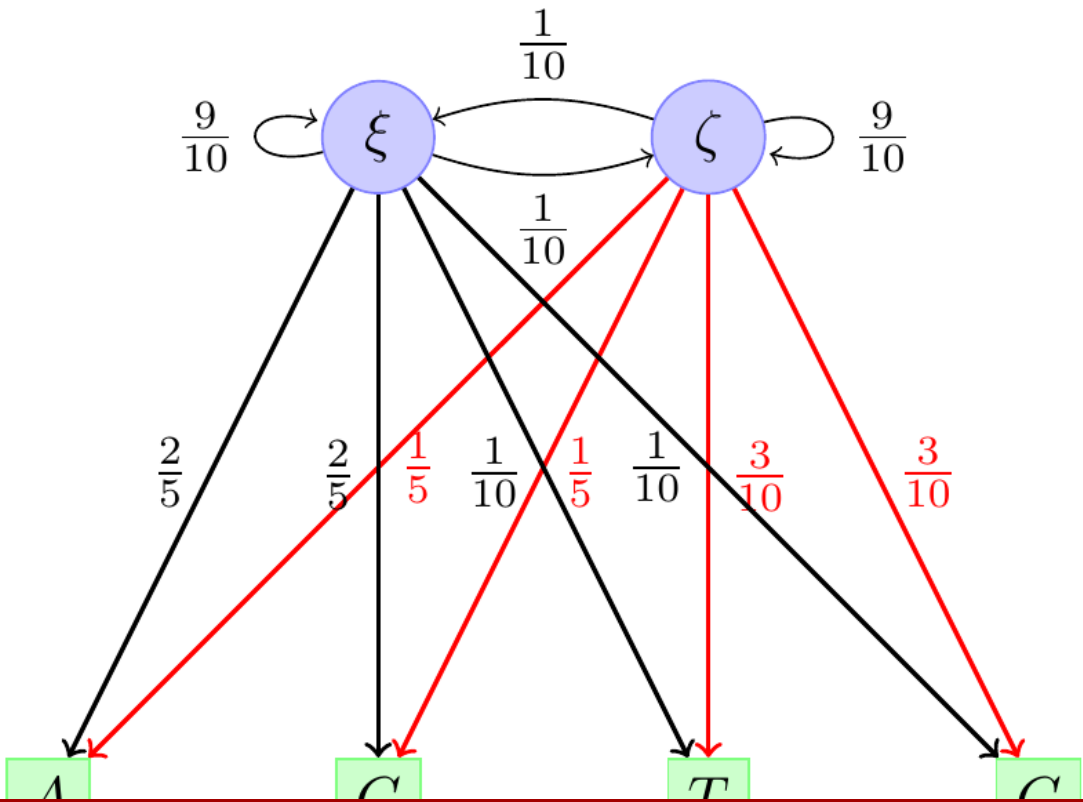
The fair casino problem

- You don't know if the dealer has a fair or unfair coin (Hidden states)
- You only observe the output (Emissions)



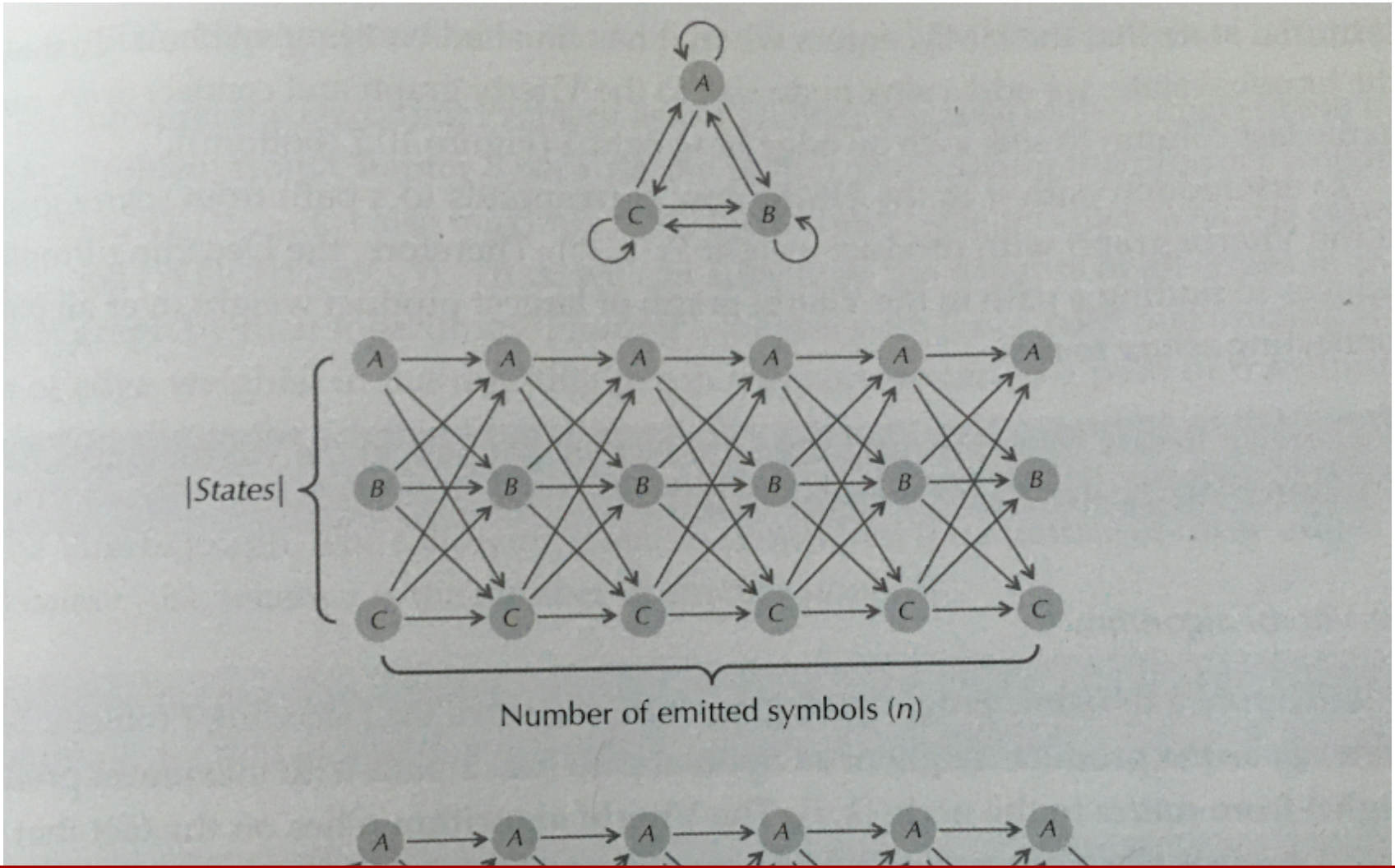
Hidden Markov Chains (Genomics)

Another (unrealistic) example is to build a HMM to describe a (genetic) sequence



Is this the only type of model available?

Viterbi's representation HMMs



Building a HMM

From Baker et al. 2014

> *Here, we present a study that identifies transient networks of brain activity, with no prior assumptions on the brain areas or time scales involved. This uses a distinct methodology based on a hidden Markov model (HMM), which infers a number of discrete brain states that recur at different points in time. Each inferred state corresponds to a unique pattern of whole-brain spontaneous activity, which is modeled by a multivariate normal distribution and a state time course indicating the points in time at which that state is active. These two outputs are shown schematically in Figure 1, and allow us to describe both the spatial and temporal characteristics of each inferred state.*

Is this the only type of model available?

Building a HMM

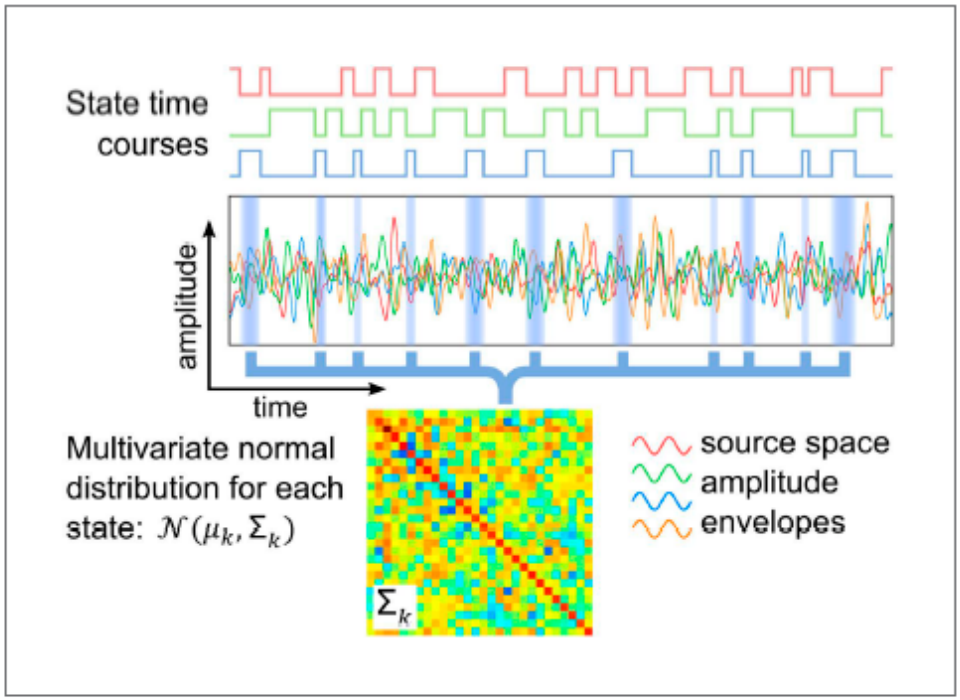


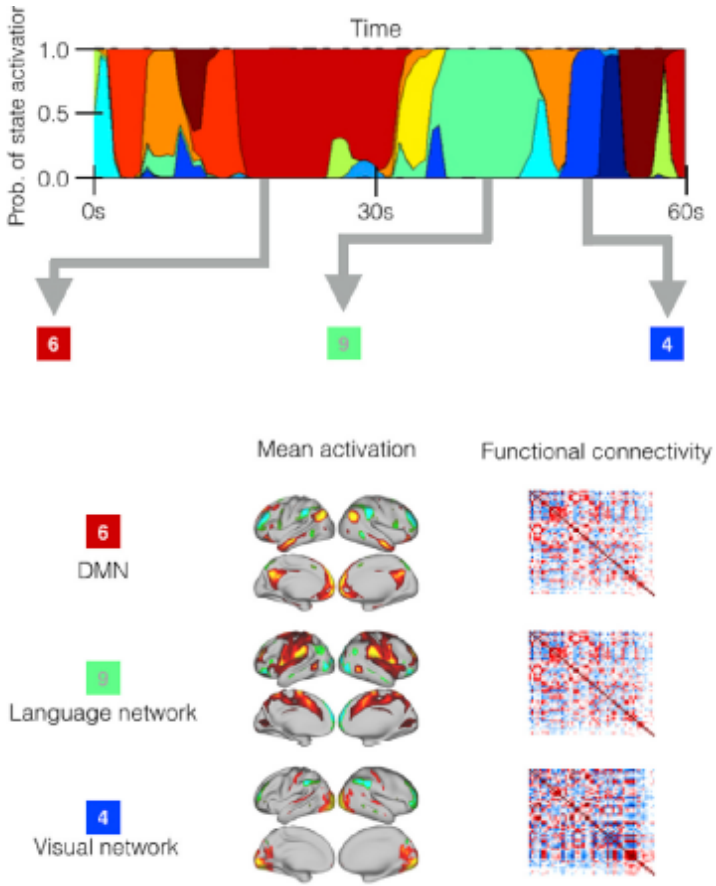
Figure 1. Schematic of the HMM outputs. An HMM with K states is inferred from band-limited amplitude envelopes of source reconstructed MEG data. Each state is characterized by a multivariate normal distribution (defined by means μ_k and covariance matrix Σ_k) and a state time course, which is a binary

In the paper

The HMM is a family of models that can describe time series of data using a discrete number of states, all having the same probabilistic distributions but each having different distribution parameters. Thus, the states correspond to unique patterns of brain activity that recur in different parts of the time series. For each time point t, a state variable dictates the probability of each state being active at that moment

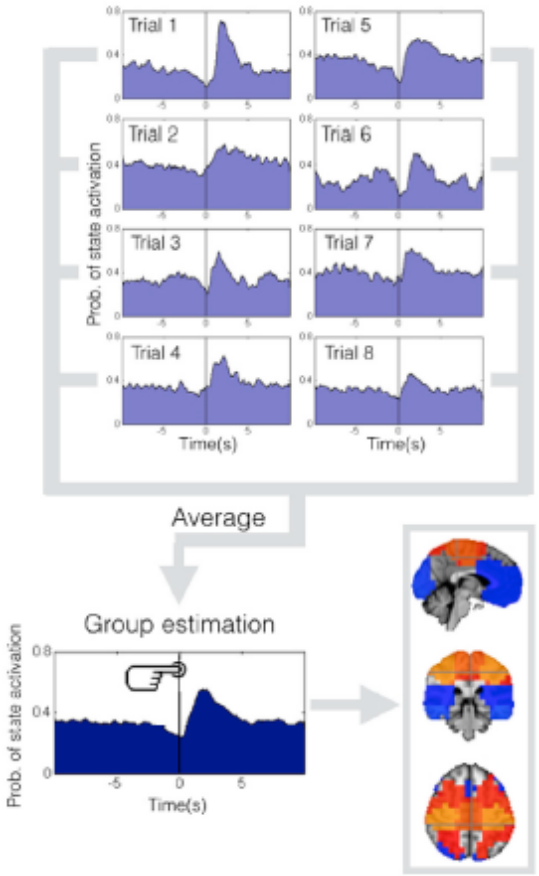
Is this the only type of model available?

General HMM at rest



Is this the only type of model available?

General HMM in task



General HMM cont

an HMM generally comprises the description of the states, the state time courses (which determines the probability of each state to be active at each time point in the time series) and the transition probabilities between the states (i.e. the probability to transition from each state to each other state). Because here we run the HMM on all concatenated subjects' datasets, the states and the transition probabilities are defined at the group level; the state time courses are however particular to each subject - that is, states can come active at different moments for each subject. Since the probability distribution of each part of the model depends on all others, there is no closed-form solution available