Digital epidemiology for the study of fertility and menstrual health

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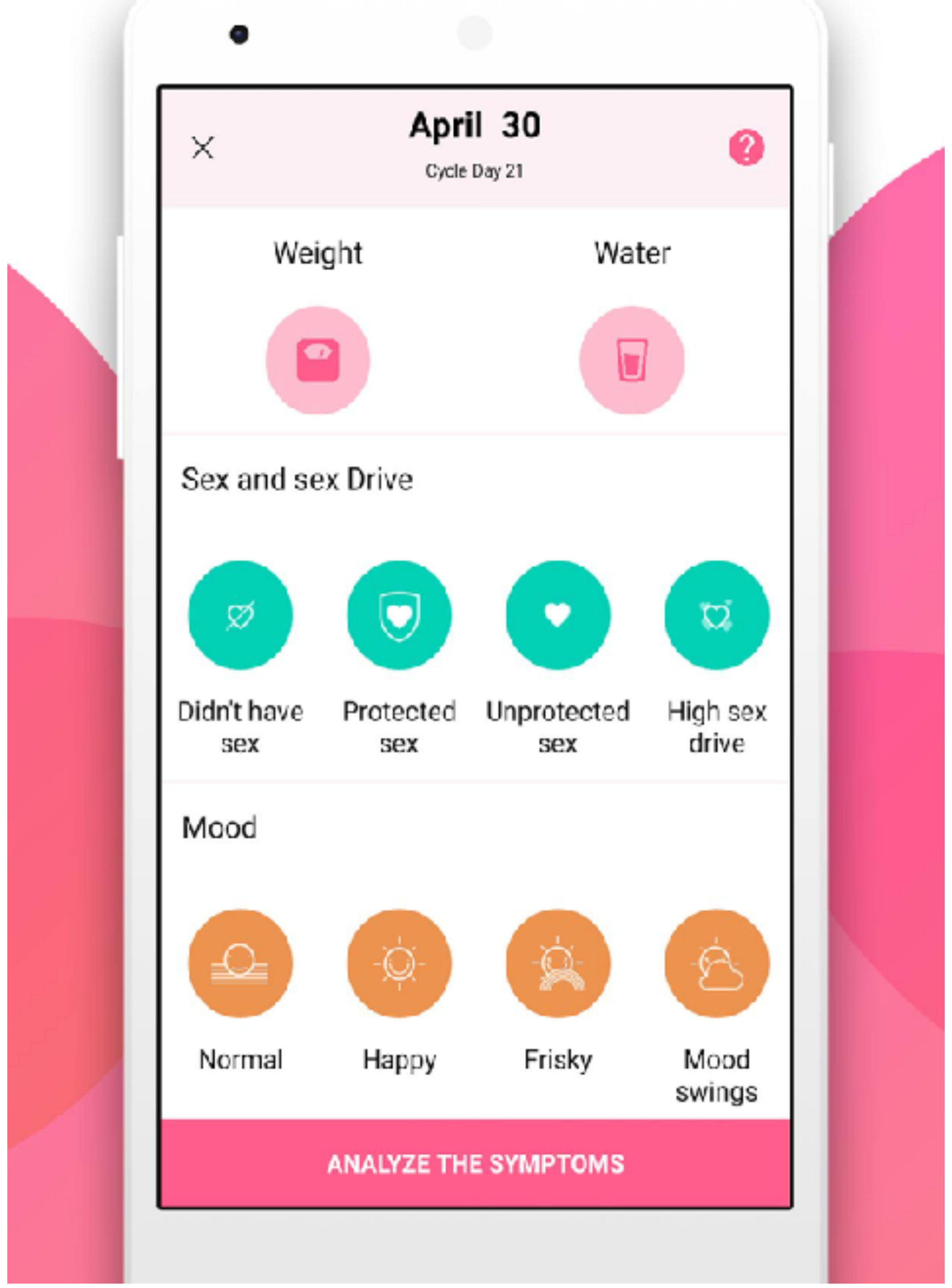
Boston University - ML for PH

Outline

- **Introduction: tracking the menstrual cycle and fertility**
- **A. Digital epidemiology for fertility**
    - Human births seasonality
    - Tracking fertility
    - Unsupervised labelling of time series of self-reported body signs
- **B. Digital epidemiology for menstrual health**
    - Trajectories of symptoms
- **Q&A**

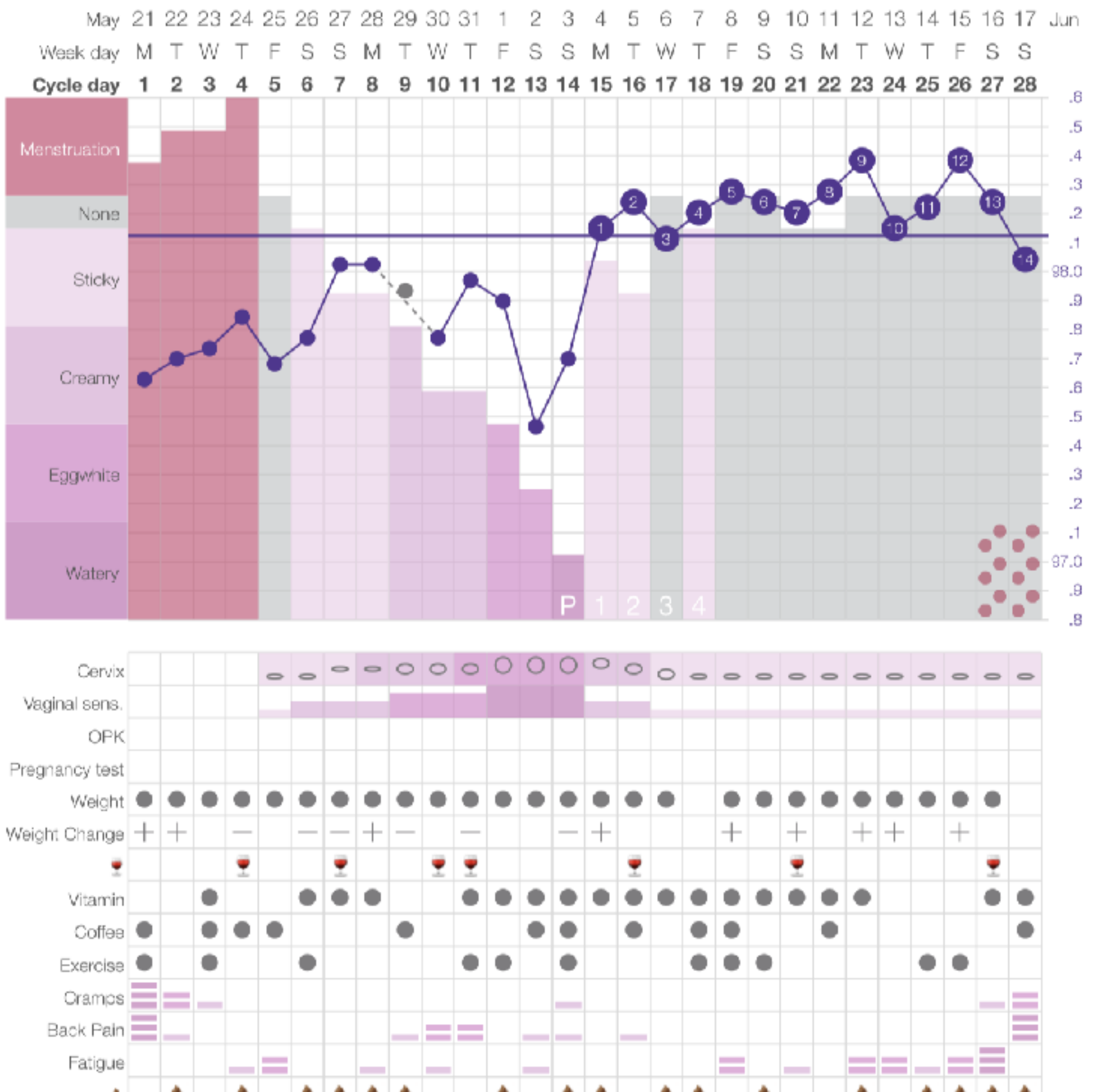
Introduction

Clue



Flo

Kindara



Tracking purposes vary a lot within users (over time) and between users. For example, users of these app may want to:

- Anticipate the **next period**
- Understand the temporal patterns of **psychological symptoms (PMS, PMDD)** and anticipate them (e.g. prepare coping strategies in advance)
- Have a **contraceptive reminder** and logging intake/administration
- Tracking **health in general** (and potentially look for association with the menstrual cycle)
- **Getting pregnant**
- **Avoid a pregnancy**

Menstrual Cycle 101
Menst. phases
Follicular phase
Luteal phase
Hormonal levels
day 1
LH
Ovulation
Progesterone
day 1
Estradiol
FSH
Inflammation
Ovarian cycle
Dominant follicle
Egg
Corpus luteum
Uterine cycle
Endometrium
Fertility-related body signs
Menstruation
Cervical mucus
Basal body temperature
~0.35C
Period
Fertile window
PMS/PME/PMDD
Period

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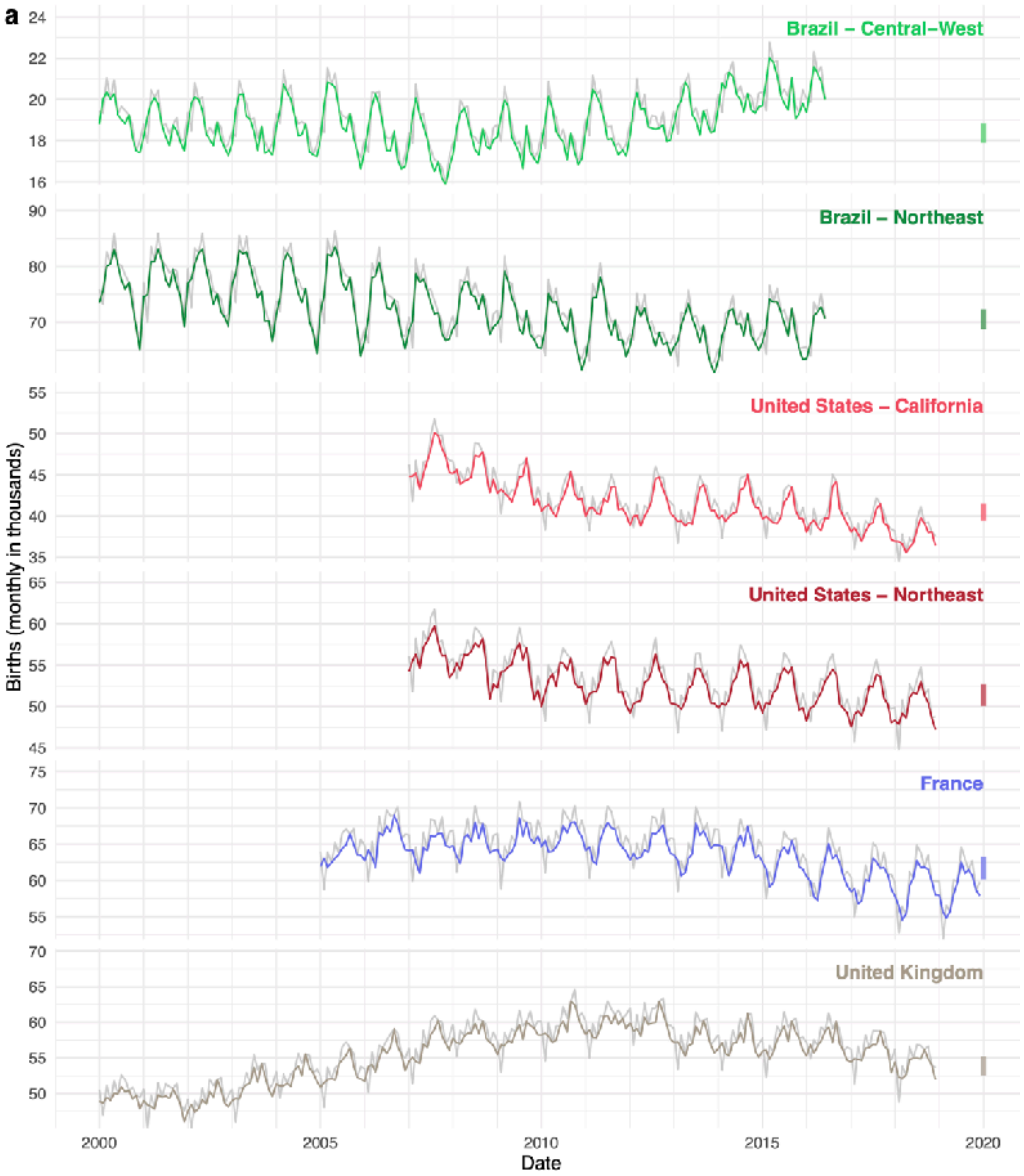
“The mysteries of human birth seasonality”



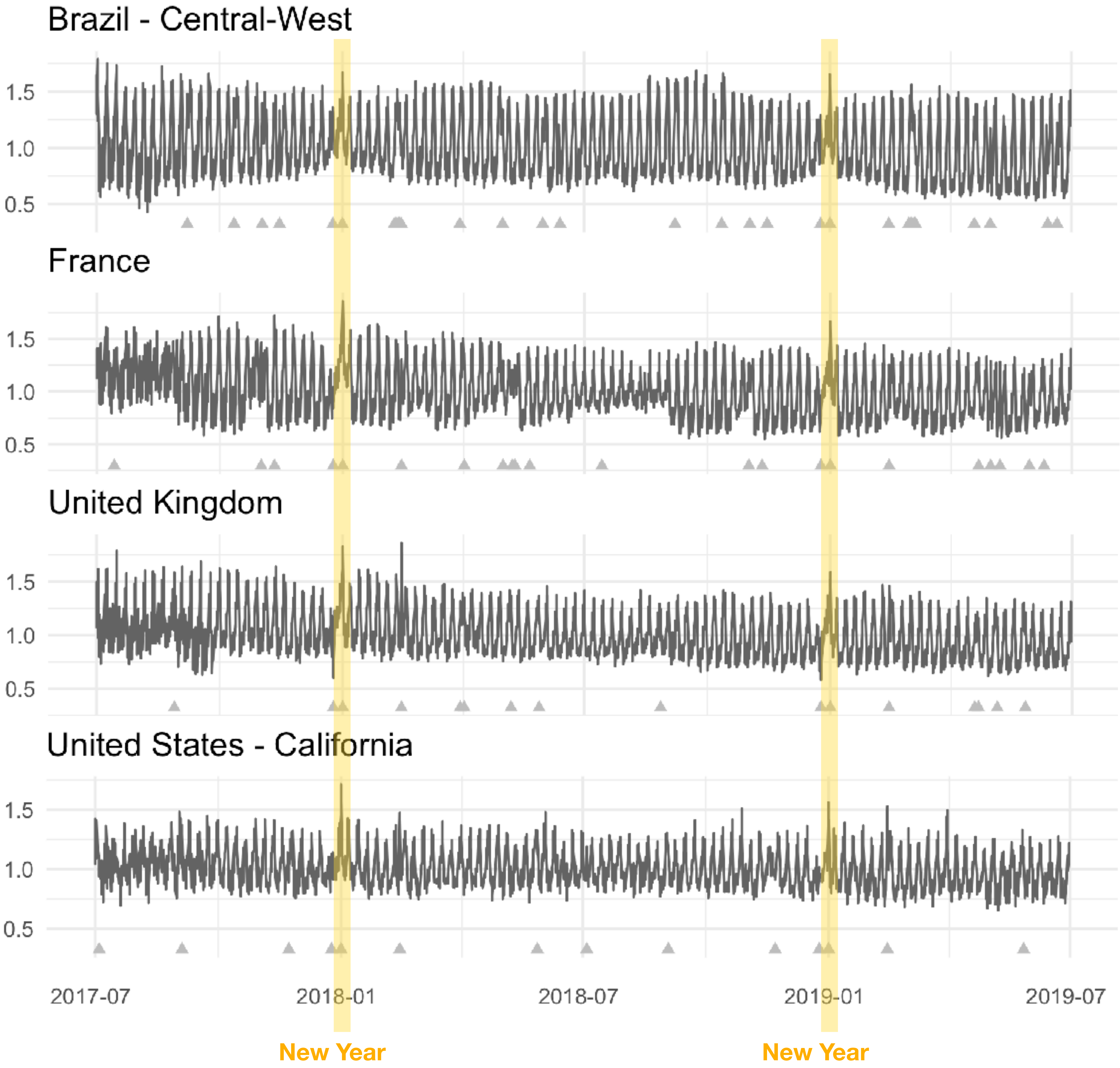
Why are births seasonal?

It could be because

1) people have **more sex** at some times of the year
2) people are **more fertile** at some times of the year

Birth rates are seasonal: there are more babies born on some months than others.
For example, in California, there are about 5000 more babies born in September than in February.

With my colleague, Prof. Micaela Martinez (Columbia University), we did an analysis of sex logs from users of the Clue app.

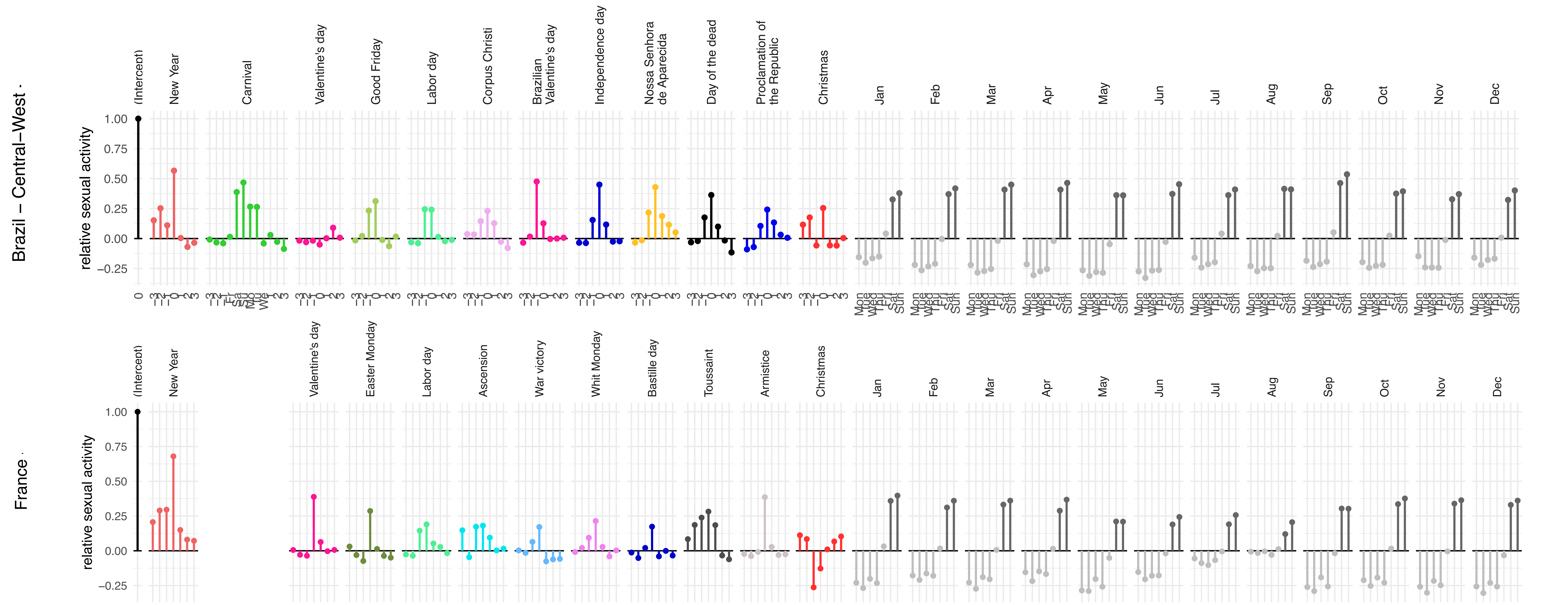


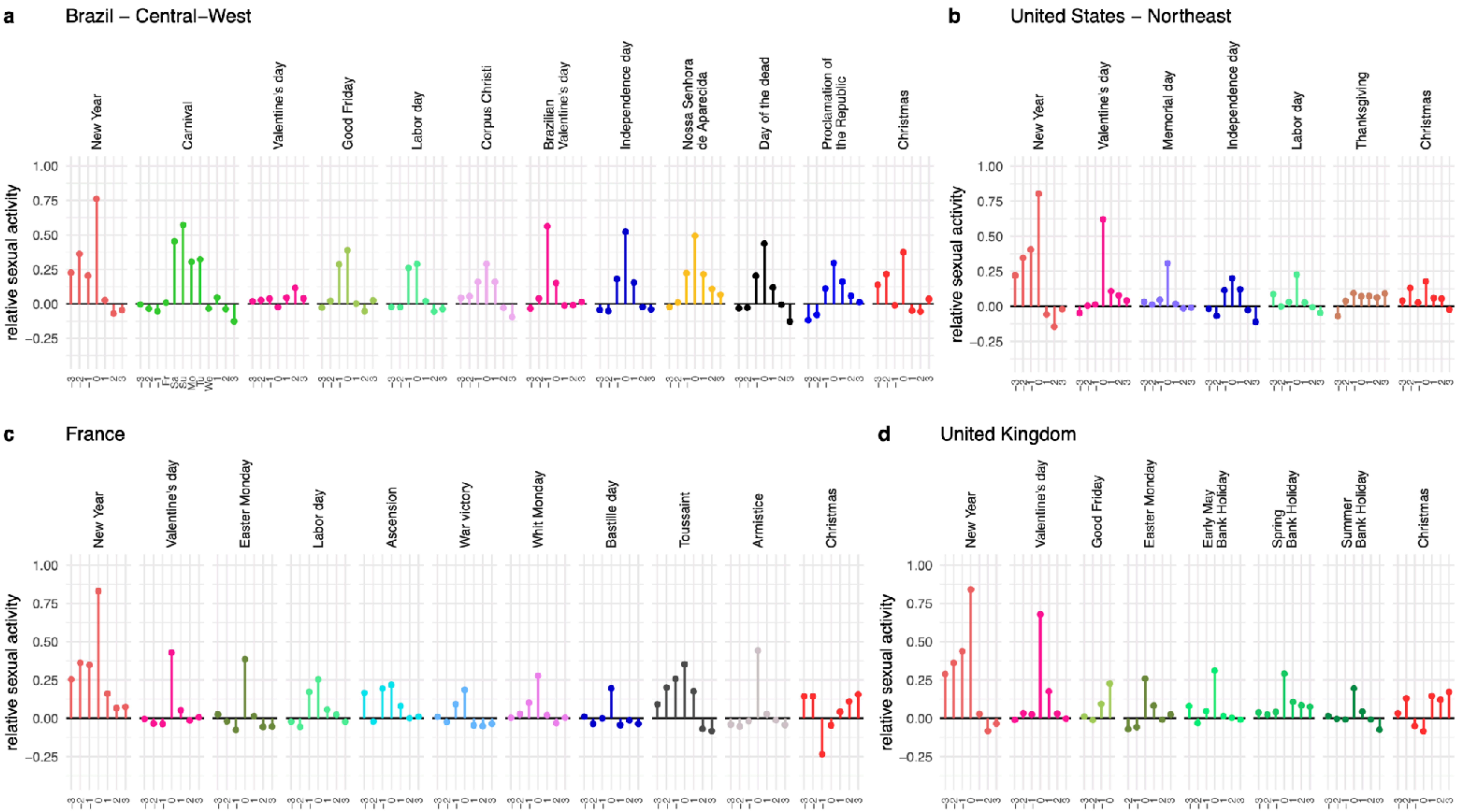
To estimate the weekly, monthly and holiday contributions to changes in sexual activity, we fit the following statistical model (linear regression) for each location

$$\mathrm{sex}[d] = \alpha i \ (\mathrm{h}[d] = i) + \beta j \ (\mathrm{wdm}[d] \ = j)$$

Where **h[d]** returns the holiday on day d. If it's not a holiday, it returns "not a holiday". If it's before or after a holiday, it returns the holiday with its -3+3 padding. For example "New Year +1" is the day after New Year, *i.e.* Jan 2nd.
wdm[d] returns the interaction between week-day and month.
For example "February x Thursday"

```
Model = glm(x ~ holiday_ID + weekday_month, data = this_cat_sex_data, family = "gaussian")
```





People have more sex at certain times of the year (on holidays) and on week-ends.

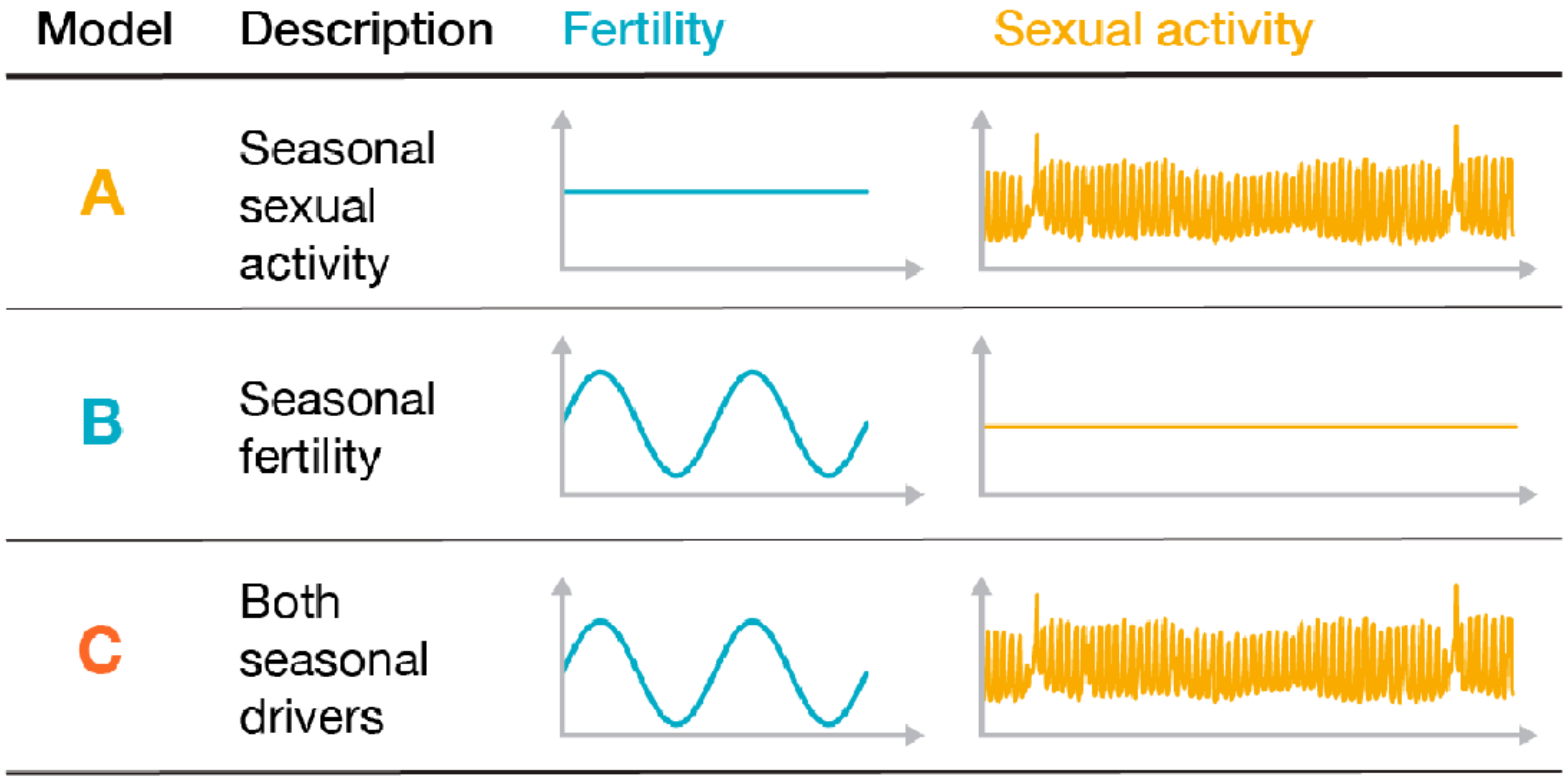
But, despite having a seasonal structure, sex cannot fully explain the shape of the birth curve.

To show that, we simulated births with 3 models:

(A) birth seasonality is driven by changes in sex activity alone

(B) birth seasonality is driven by fertility alone (modeling fertility as a sine curve)

(C) birth seasonality is driven by changes in both fertility and sex activity



Mathematical model for number of births:

$$C(t) = f(t)S(t)$$

$$B(t) = \int_{t-max(G)}^{t-min(G)} d^G(\tau)\ (1 - l(\tau))\ C(\tau)d\tau$$

where

$C(t)$ = number of conceptions at time t;

$f(t)$ is the fertility at time t (= the odds of a conception from a sexual intercourse);

$S(t)$ the number of sexual intercourses at time t;

$B(t)$ is the number of births at time t;

G is the gestation duration (i.e. the duration of a pregnancy)

$d^G(t)$ is the probability density of the gestation duration and;

$l(t)$ is the pregnancy loss rate at time t (= the fraction of pregnancies ending up in a loss).

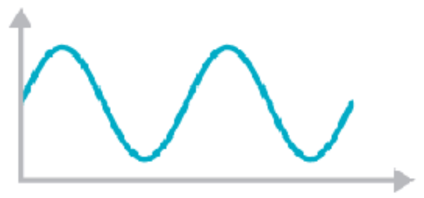
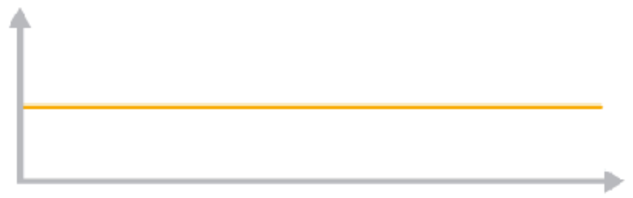
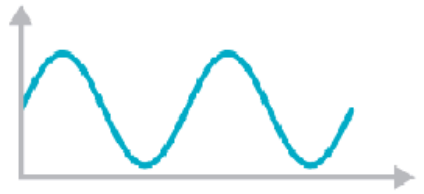
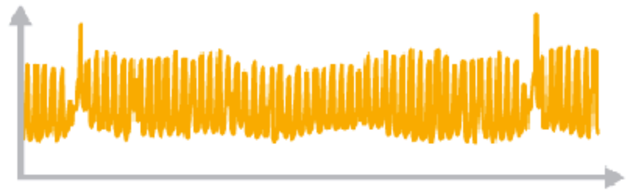
$$B(t) = \int_{t-max(G)}^{t-min(G)} d^G(\tau)\ (1 - l(\tau))\ f(\tau)\ S(\tau)d\tau$$

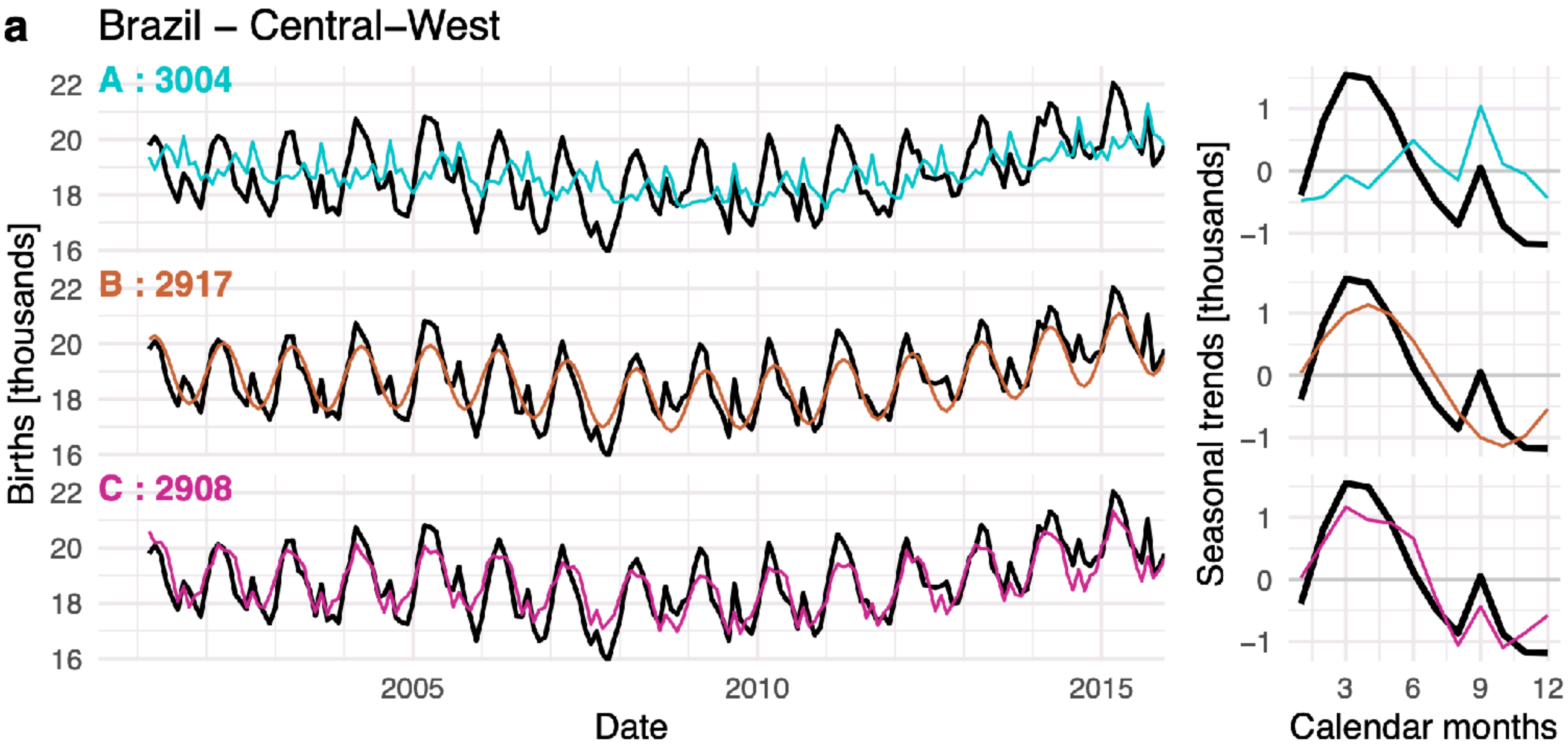
$$\Longrightarrow B(t) = \int_{t-max(G)}^{t-min(G)} d^G(\tau)\ F(\tau)\ S(\tau)\ d\tau$$

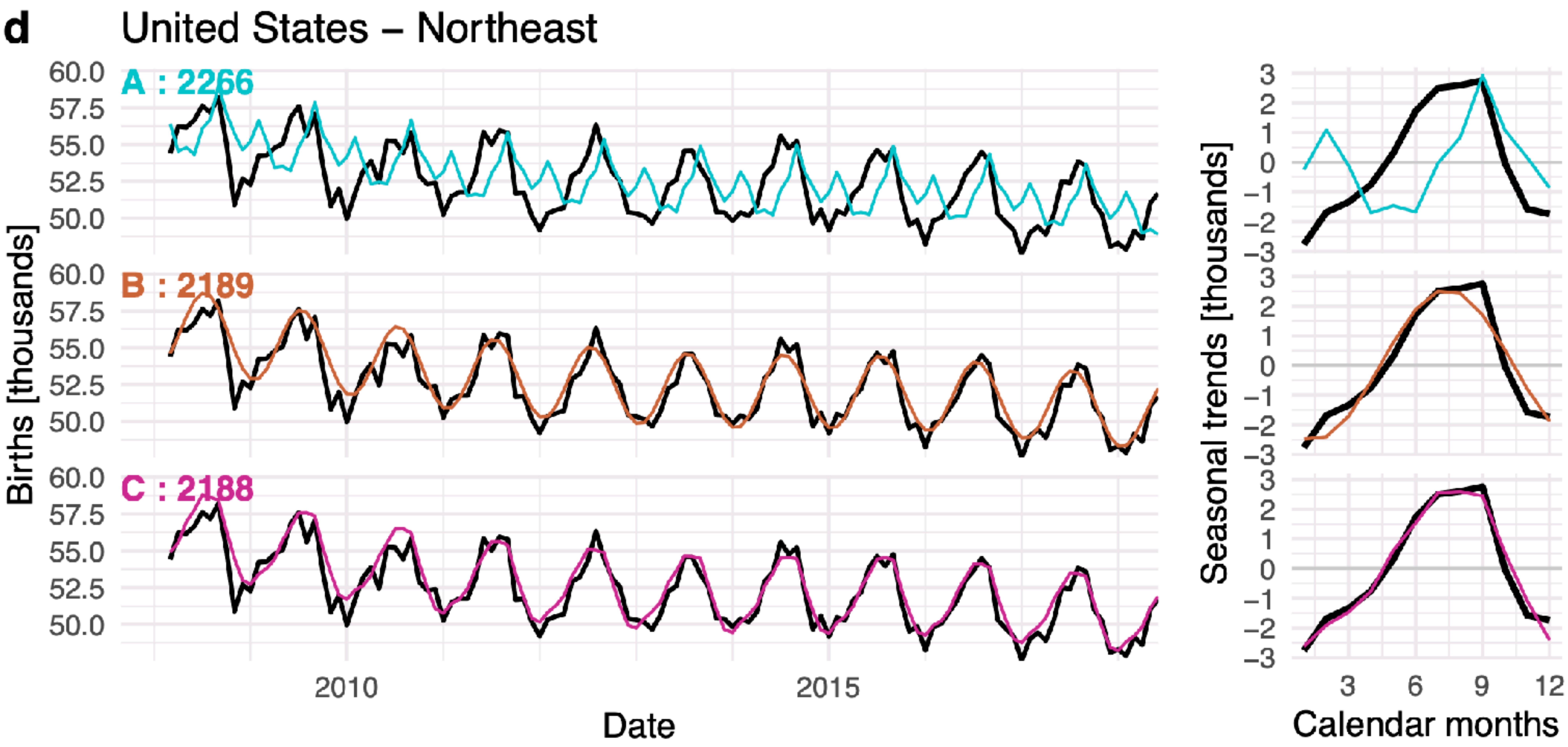
Where $F(\tau)$ is a function combining fertility and loss rate.

In discrete time-steps, the model becomes:

$$B_t = \sum_{\tau=t-max(G)}^{t-min(G)} d_\tau\ F_\tau\ S_\tau$$

Model	Description	Fertility	Sexual activity
A	Seasonal sexual activity		
B	Seasonal fertility		
C	Both seasonal drivers		


a
Brazil – Central–West
A : 3004
B : 2917
C : 2908
Births [thousands]
22
20
18
16
2005
2010
2015
Date
Seasonal trends [thousands]
1
0
−1
3
6
9
12
Calendar months



Conclusions:
Seasonal fertility seems to exist and account for a large part of the variations in birth seasonality.

The next question is:
Is male and/or female fertility seasonal?

Could we use **fertility app** data to answer these questions?

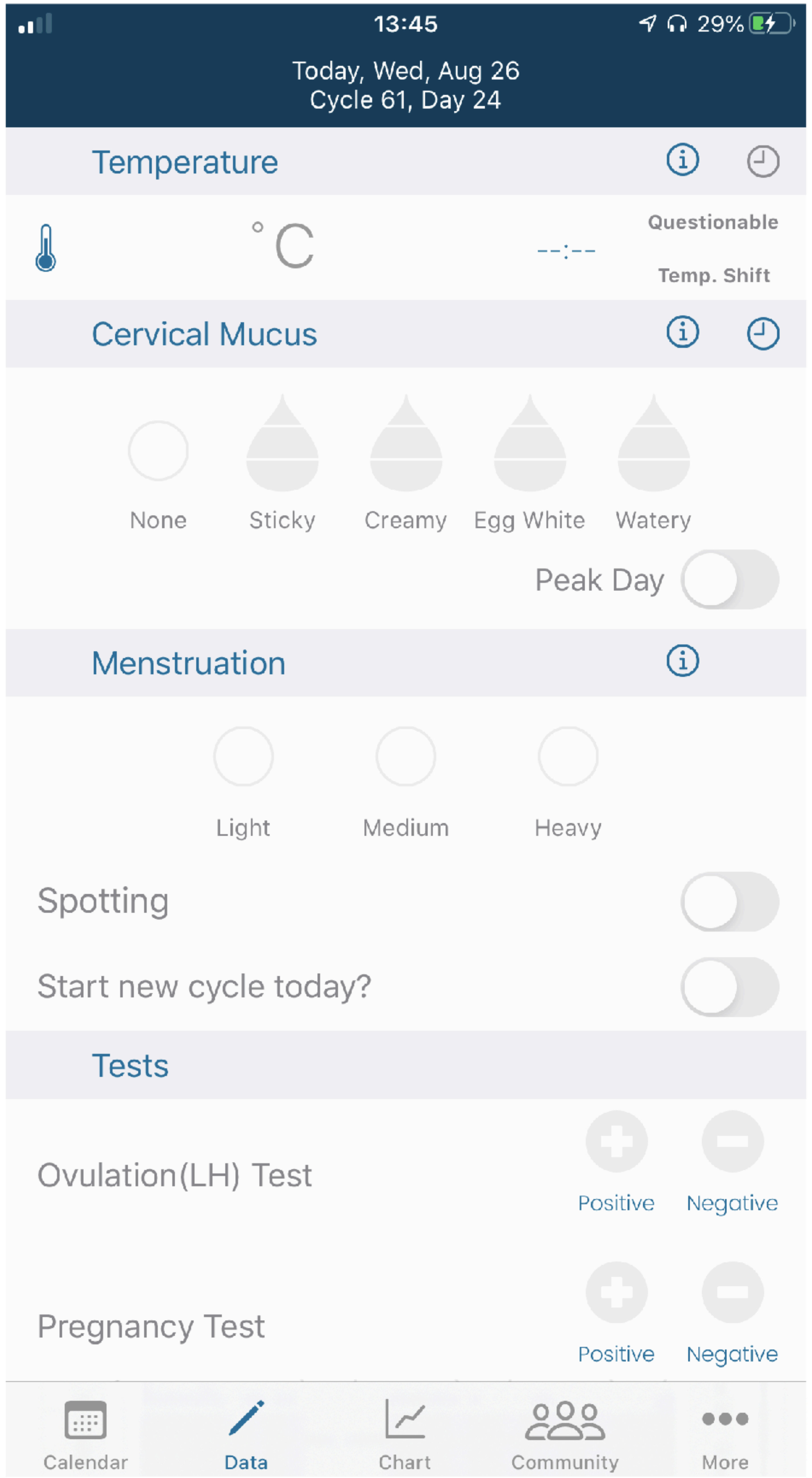
Before using these data, **we need to check** that **the observations** from past medical studies on small cohorts were also observed in this massive cohort of self-selected subjects.

1. Do we observe a **rise in temperature** after ovulation?
2. Do we observe a **change in self-observed and self-reported cervical mucus**?
3. Can we **estimate the timing of ovulation** from these self-reported data?
4. Does the **distribution of ovulation day** match the distributions reported by previous studies?

We used data from two fertility apps to do these checks

sympto FREE — sympto — **N = 13,000**

Kindara — **N = 200,000**



Long term tracking of 2 app users (top user likely sub-fertile; bottom users: pregnancy)

Fertility awareness body-signs: aggregates from 750k+ cycles

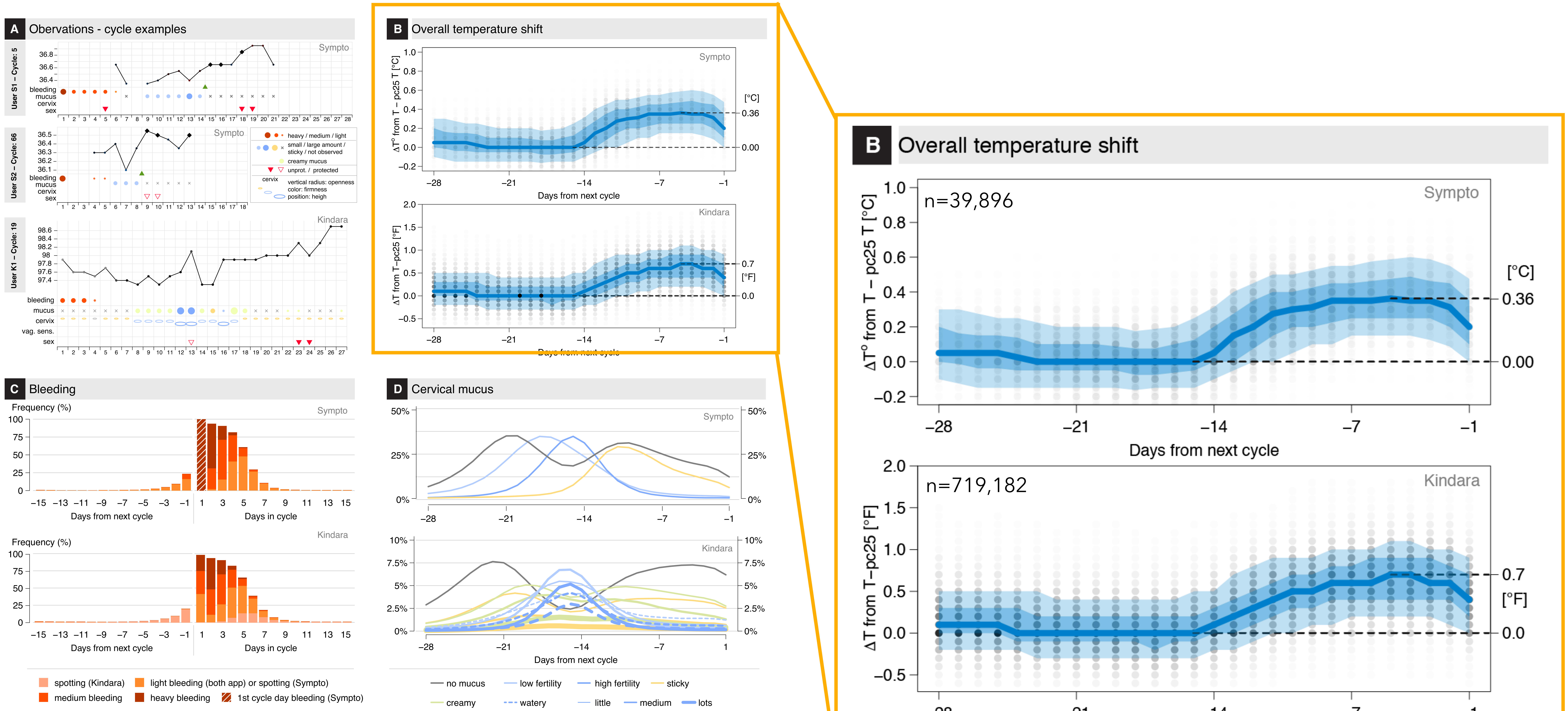
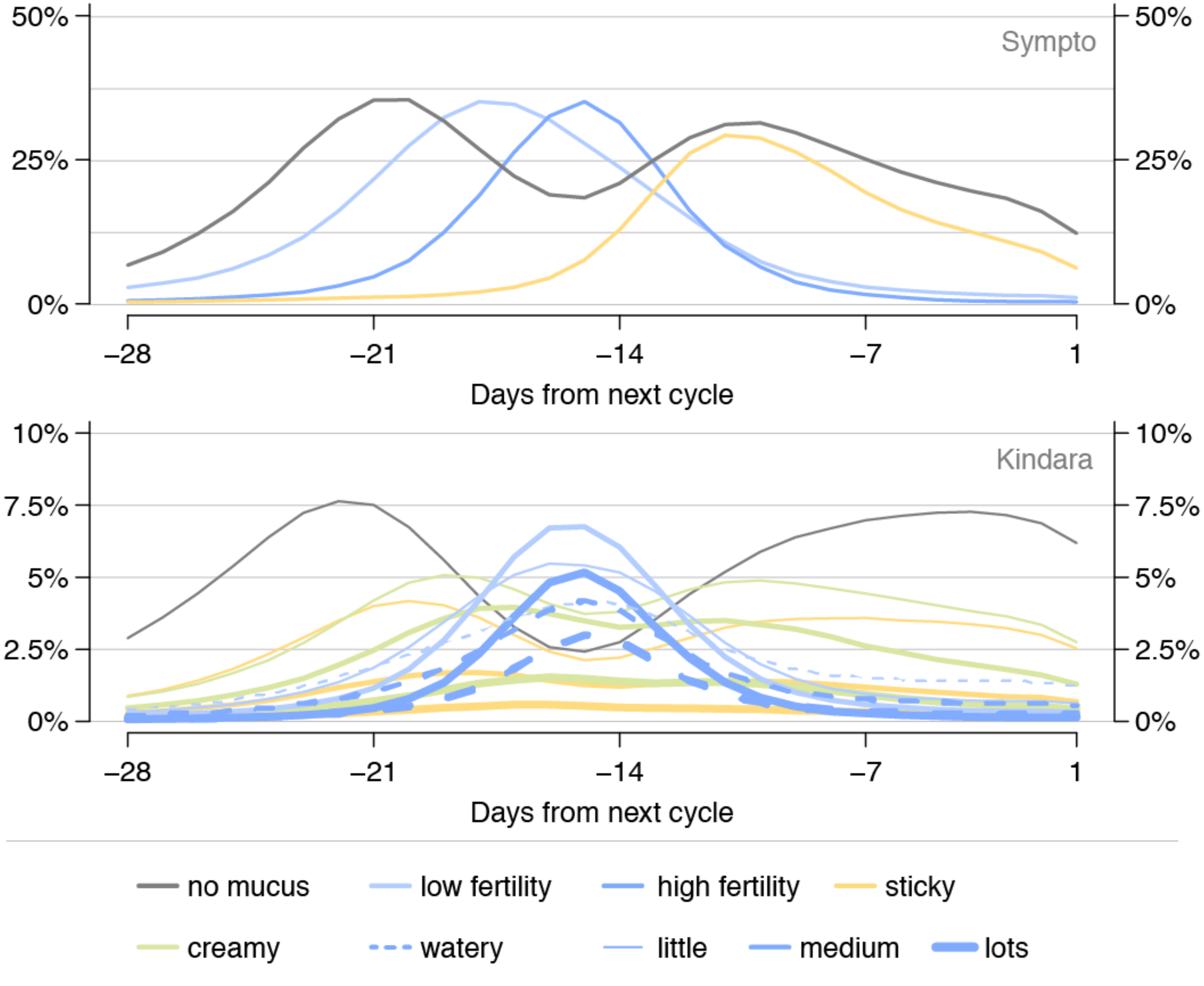
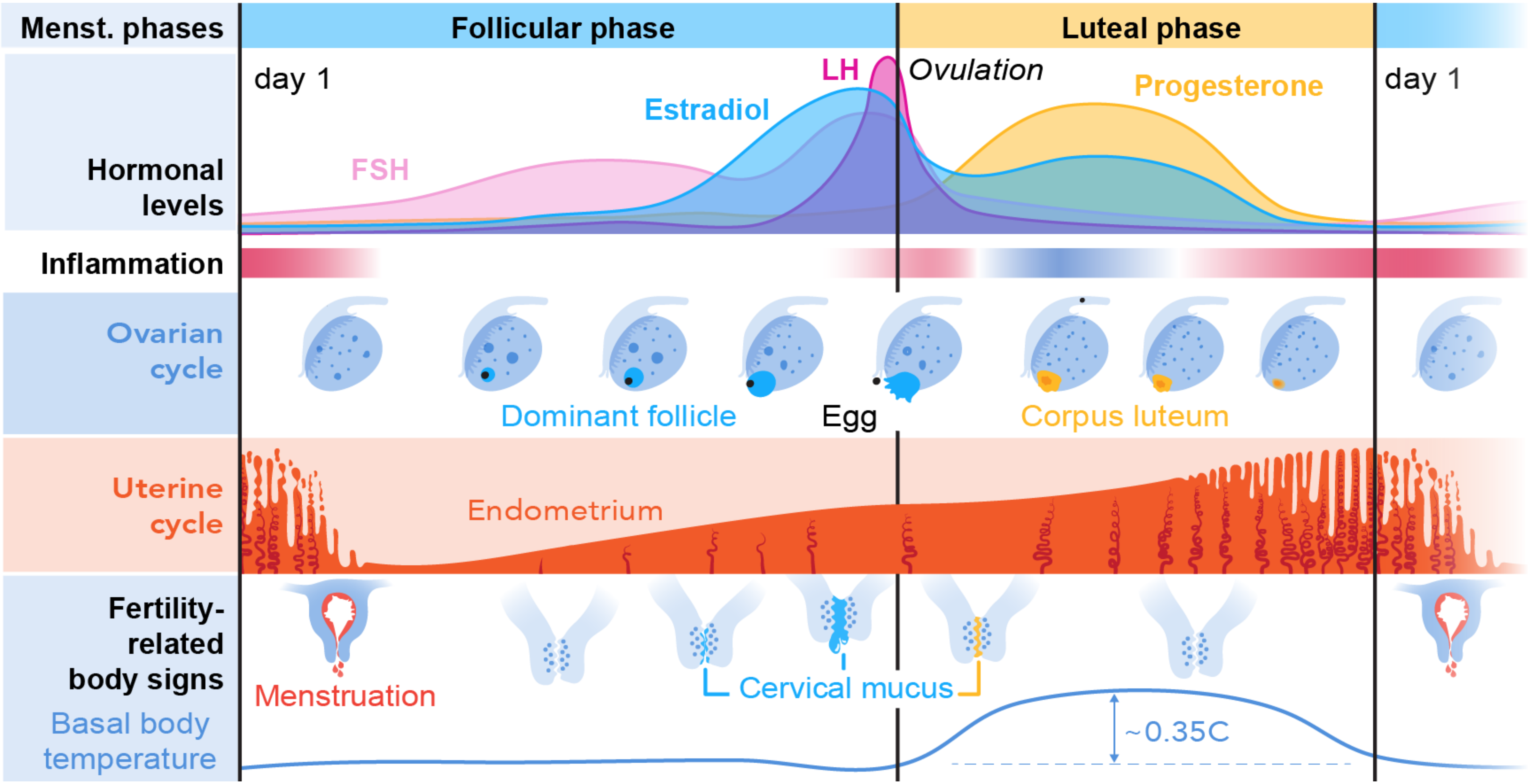


Fig. 3 User observations overview. **a** Examples of observations: the 5th tracked cycle (top) and 66th cycle (middle) cycle of two different Sympto users. Observations of the 19th cycle (bottom) of a Kindara user. **b** ΔBBT (variation from the 25% percentile of temperature in this cycle) values are shown on each day of the cycle, from the end of the cycle. Opacity of the dots reflects the number of observations. The median value: thick blue line. 10, 25, 75, and 90 percentiles of ΔBBT: translucent blue bands. **c** Frequency of bleeding observations, for the end (left) and beginning (right) of cycles. The Sympto app only starts a new cycle on the first recording of heavy bleeding (score 3/3, dark red) after a post-ovulatory infertile phase, thus all cycles present heavy bleeding at the start of the cycle (hashed dark red bar). **d** Frequency of cervical mucus observations from the end of cycles (top: S, bottom: K). (Kindara) Little quantity of watery mucus (dashed line) and little or medium quantity of egg-white like mucus (solid line) are considered as "low fertility" mucus (light blue) while large quantities of egg-white like and medium or large quantities of watery mucus are considered as "high fertility" mucus (dark blue) (B-D) 39,896 (S) +719,182 (K) *standard cycles* were used (Methods)

D Cervical mucus

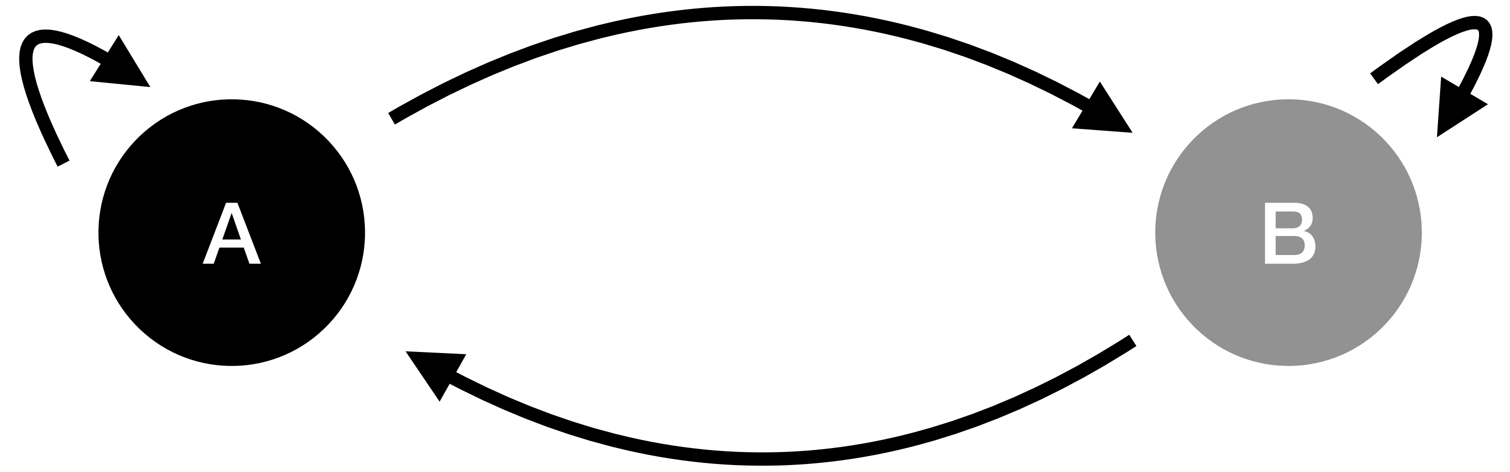


From these data, can we estimate the timing of ovulation without making any prior assumption on this timing?



Introduction to hidden states models

The simplest state models are Markov Models



	A	B
A	0.9	0.1
B	0.1	0.9

AAAABBBBBBBAAAAAAAAAAABBBBBAAAAAABAAA

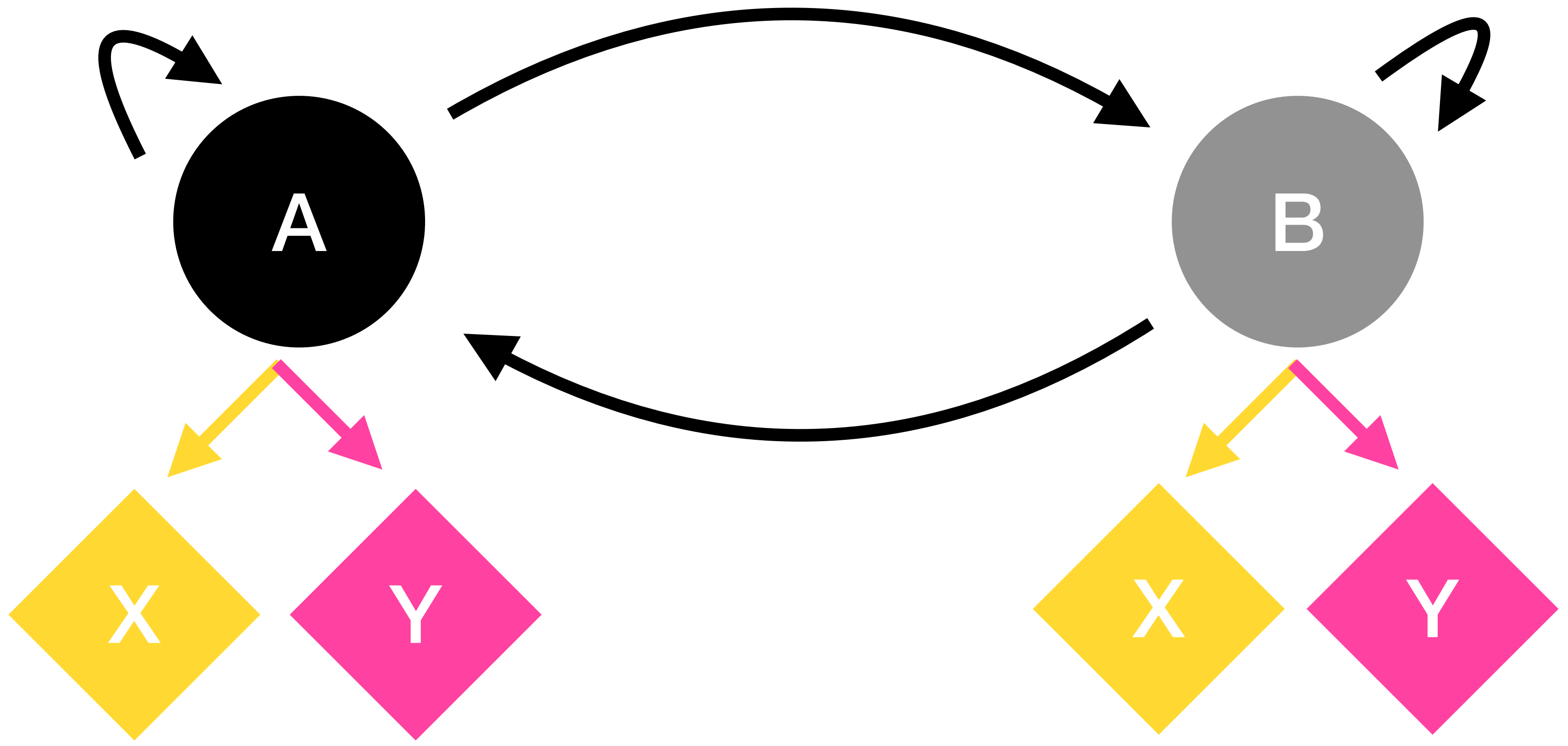
	A	B
A	0.1	0.9
B	0.9	0.1

ABBABBAABAAABABABABABBABABBAAABABABAB

	A	B
A	0.9	0.1
B	0.9	0.1

AAAAABAAAAABAAAABBAAAAAAABAAAAAAABAAA

The simplest hidden state models are Hidden Markov Models (HMM)

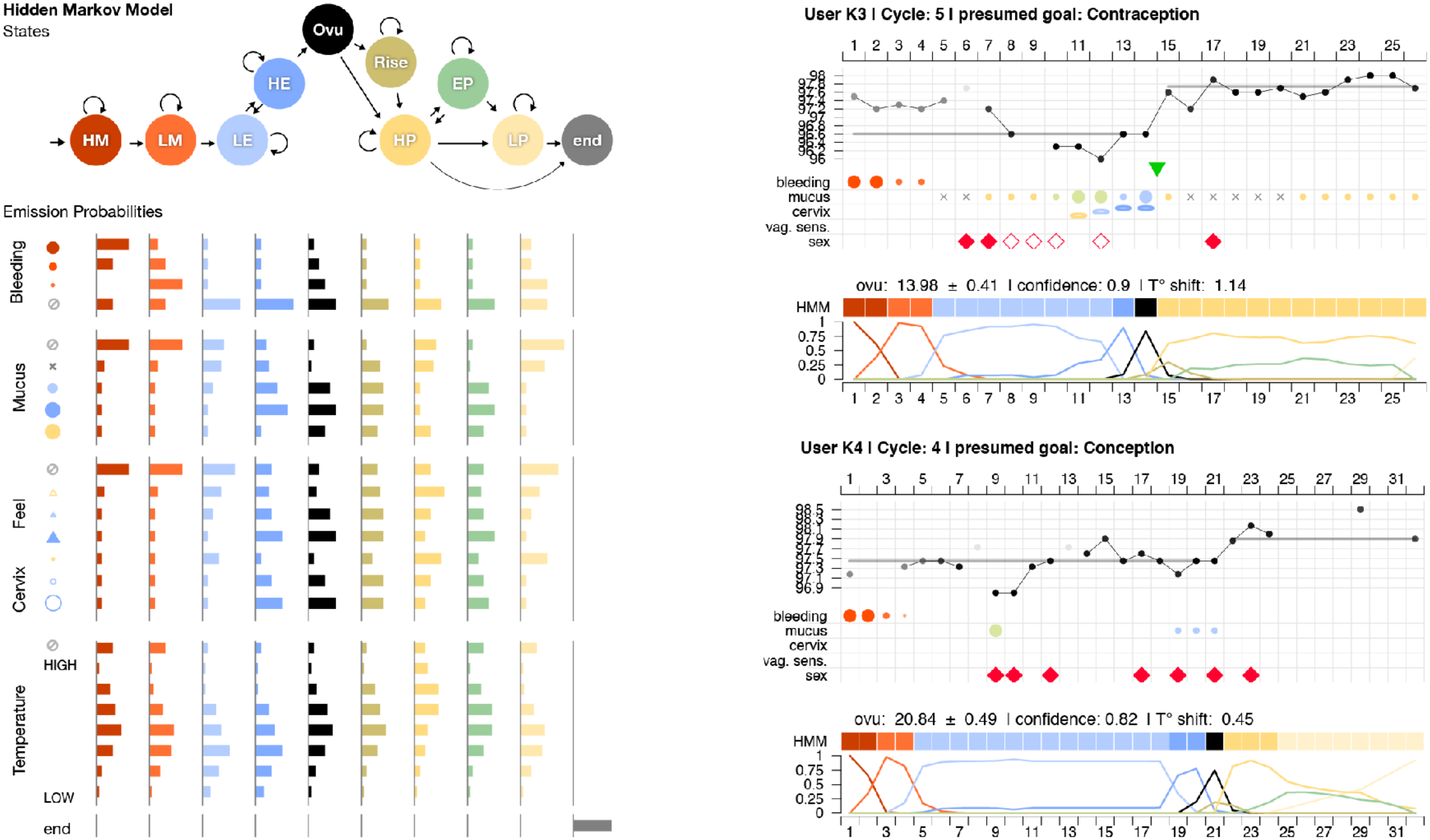


	A	B
A	0.9	0.1
B	0.1	0.9

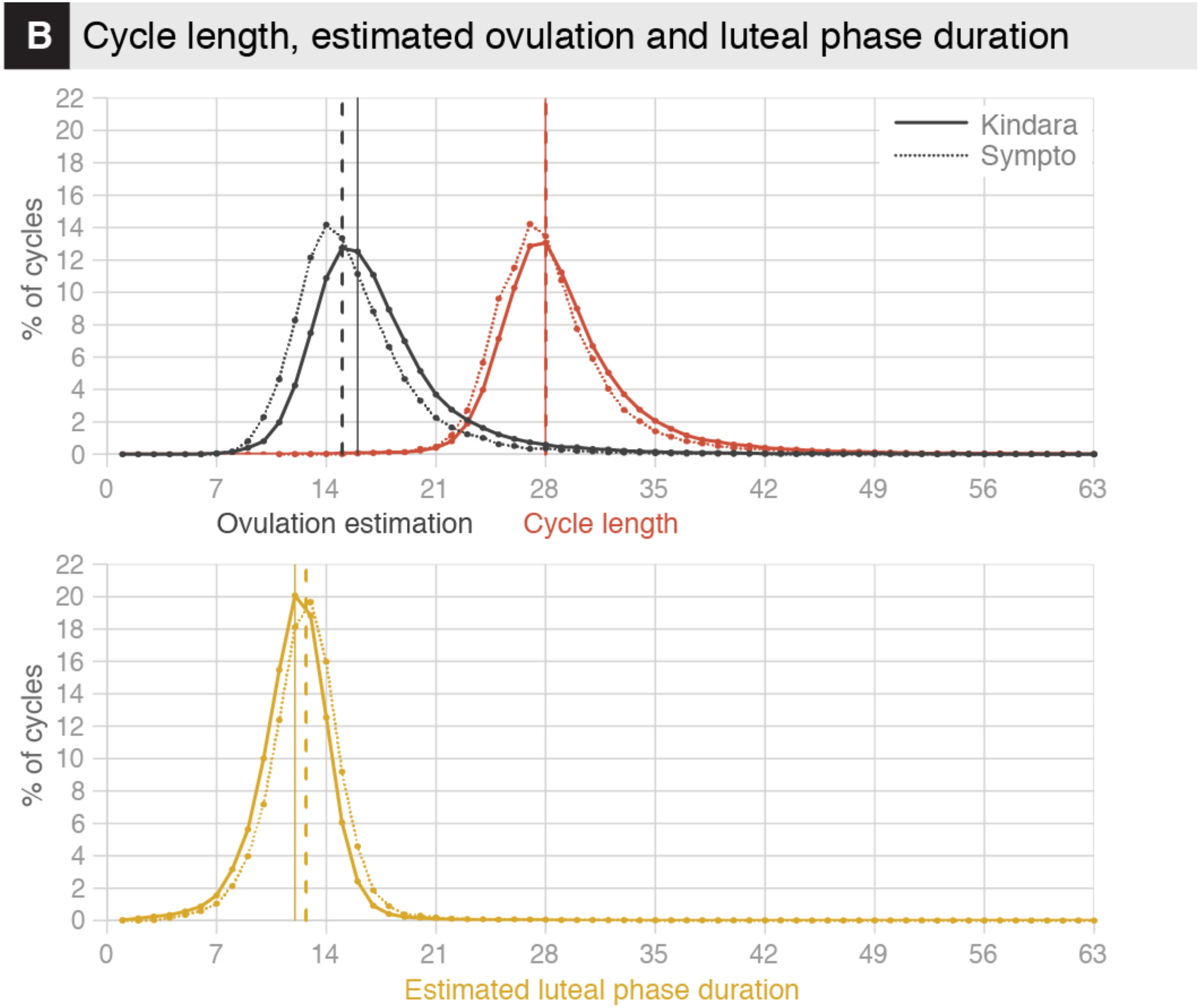
	X	Y
A	0.9	0.1
B	0.1	0.9

AAAABBBBBBBAAAAAAAAAAABBBBBAAAAAABAAA

XXYXYYXYYYXXXYXXXYYXXXYYYYYYXYXXXYXXX

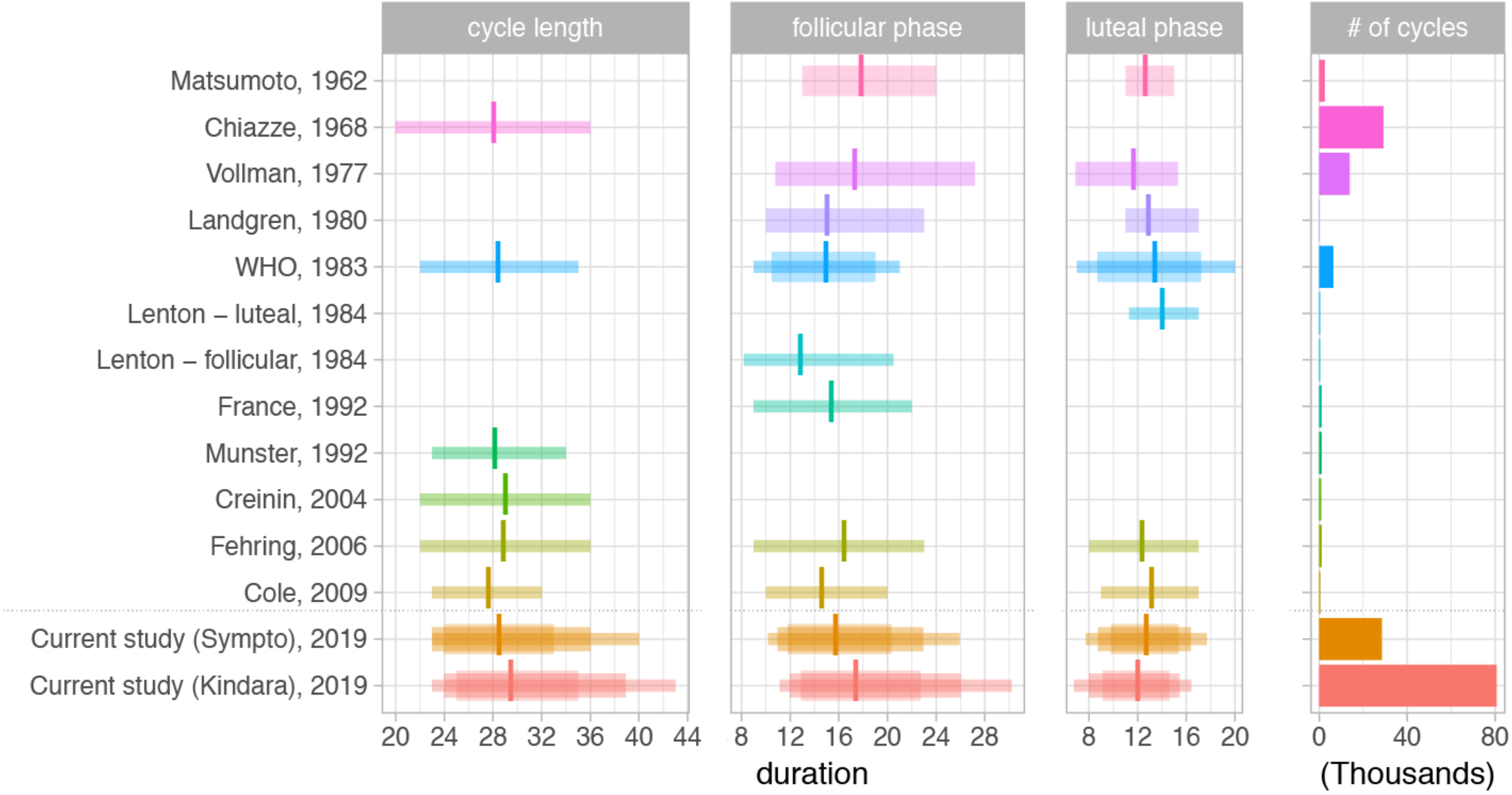


Hidden Markov Model
States
HM
LM
LE
HE
Ovu
Rise
HP
EP
LP
end
Emission Probabilities
Bleeding
Mucus
Feel
Cervix
Temperature
HIGH
LOW
end
User K3 I Cycle: 5 I presumed goal: Contraception
bleeding
mucus
cervix
vag. sens.
sex
ovu: 13.98 ± 0.41 I confidence: 0.9 I T° shift: 1.14
HMM
User K4 I Cycle: 4 I presumed goal: Conception
bleeding
mucus
cervix
vag. sens.
sex
ovu: 20.84 ± 0.49 I confidence: 0.82 I T° shift: 0.45
HMM



B
Cycle length, estimated ovulation and luteal phase duration
Kindara
Sympto
% of cycles
Ovulation estimation
Cycle length
% of cycles
Estimated luteal phase duration

Comparison of cycle phases duration and ranges with previous epidemiological studies



Conclusion: **when** users report their body signs, they match expected patterns really well.

BUT… still some problems to solve if we want to use these data for studies of fertility.

For example, we need to be able to:

1. **Detect early pregnancies**, even in the absence of pregnancy test results
2. Differentiate pregnancies from **tracking interruption**
3. Differentiate early pregnancies from **long cycles**
4. Estimate the **timing of ovulation in all cycles**, relying on priors when self-reports are not available.
5. **Adapt to changes in tracking purposes** (and thus tracking frequency and/or changes in reported variables)

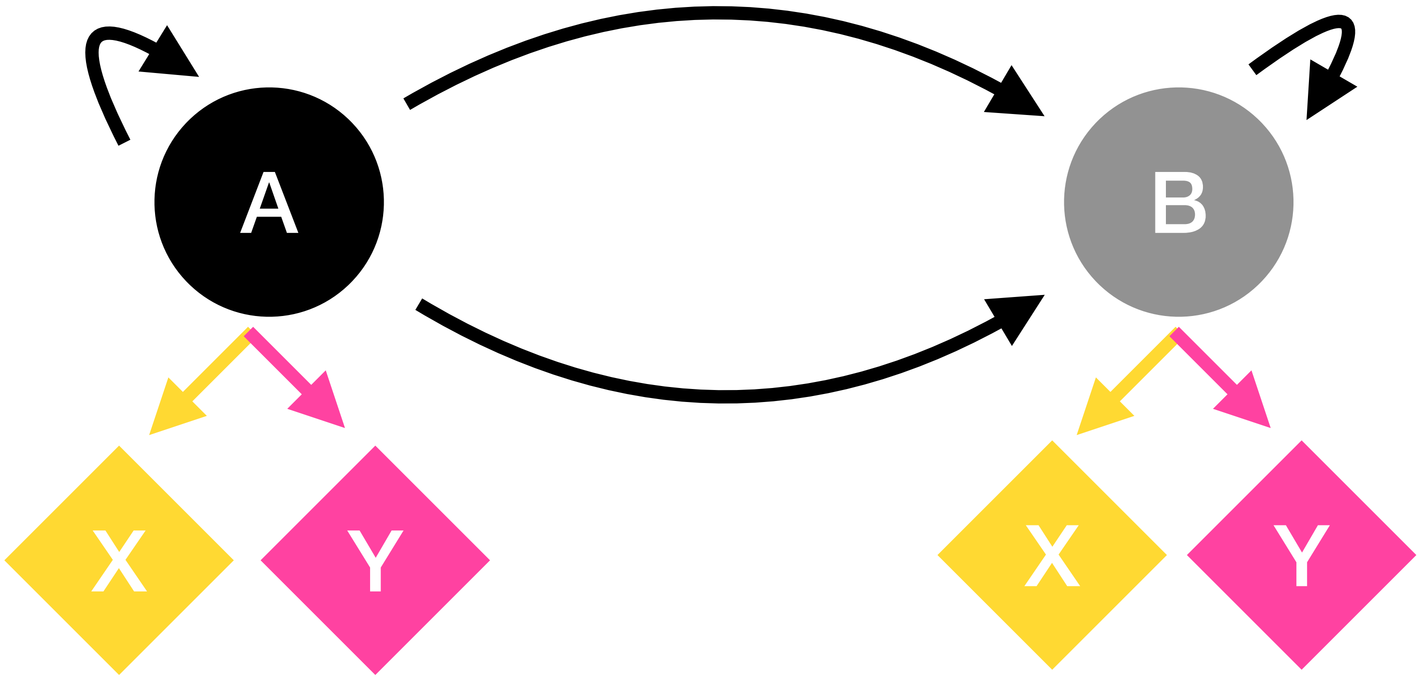
How do we identify and count pregnancies and pregnancy losses?

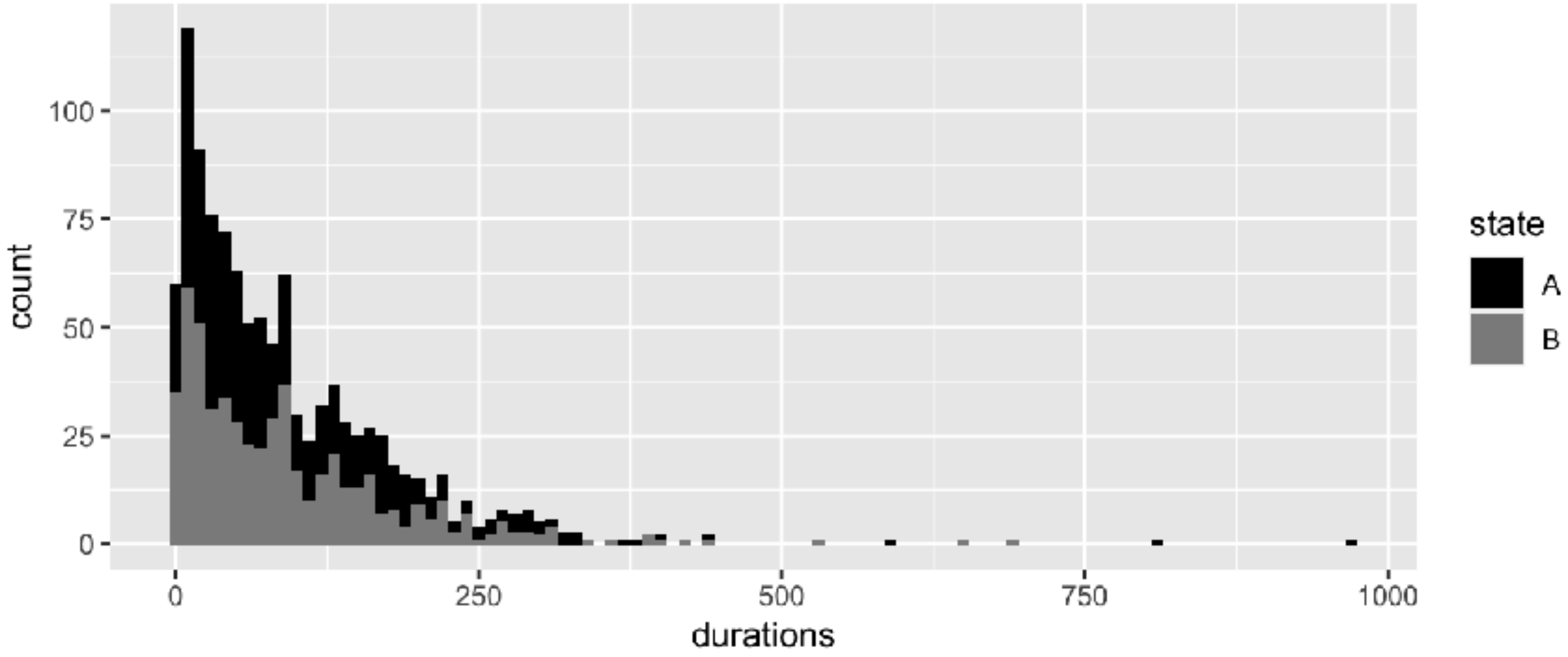
Task description:

- Biologically meaningful labels
- Ideally, we want to quantify uncertainty on our labels
- No ground truth available
- Many missing data
- Method needs to work on multivariate time-series with variables of different type (continuous, discrete, categorical)

Introduction to hidden semi-Markov models

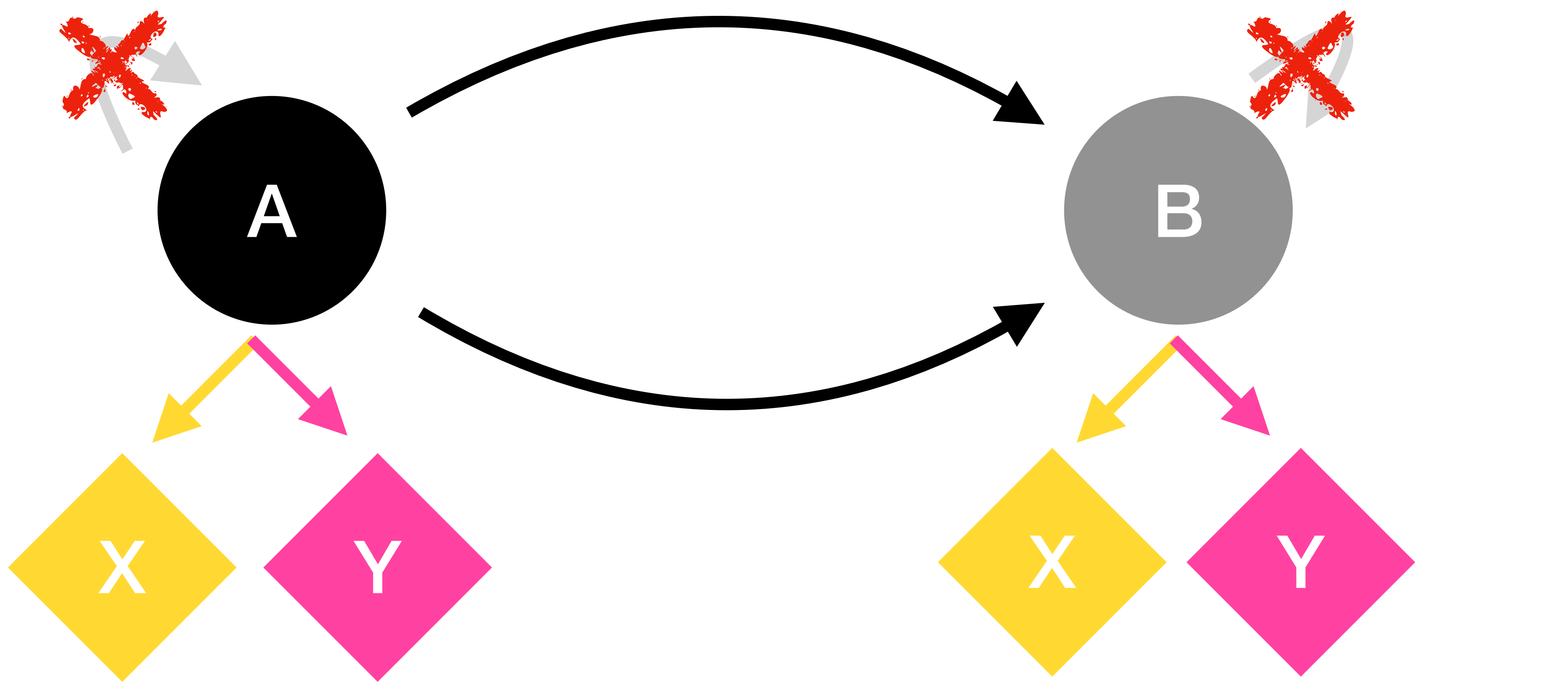
Markov models have a 1st order memory:
The state at time *t* only depends on *t-1*.
Everything before t-1 is irrelevant.

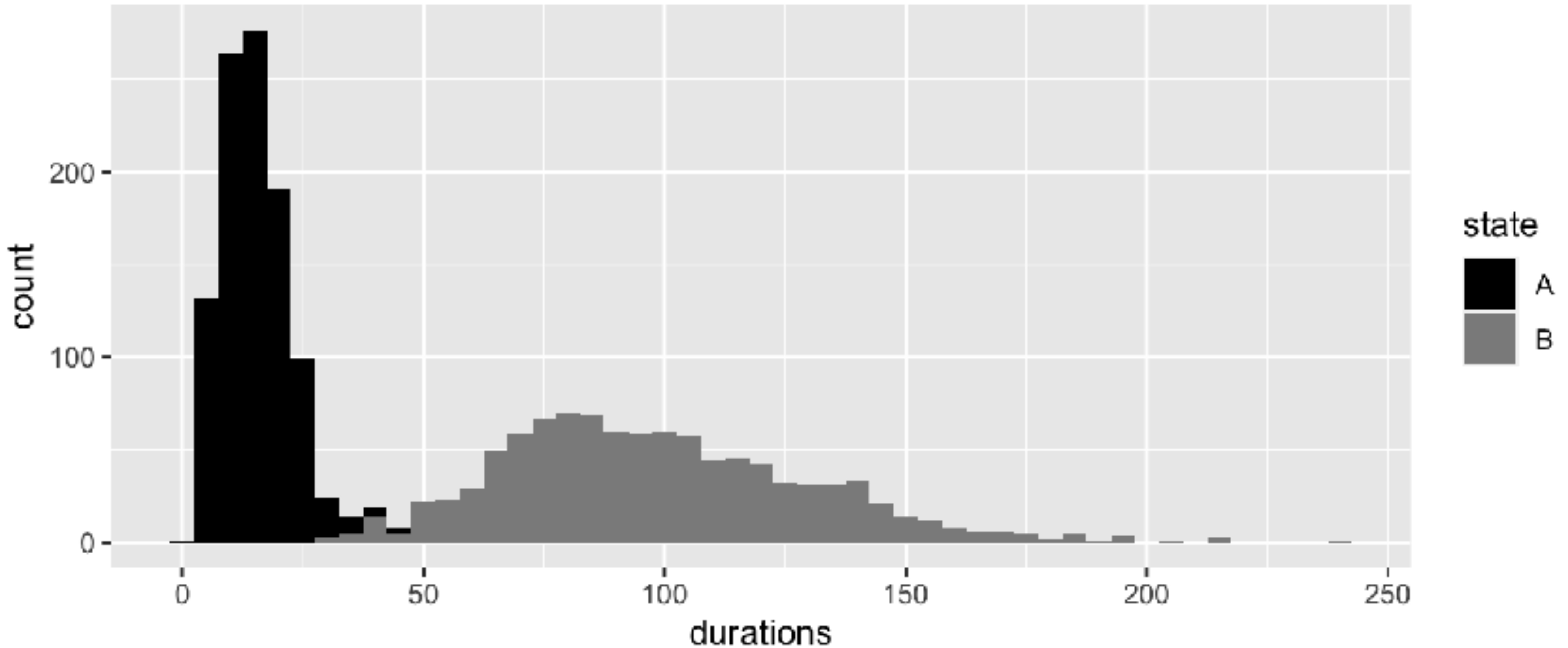


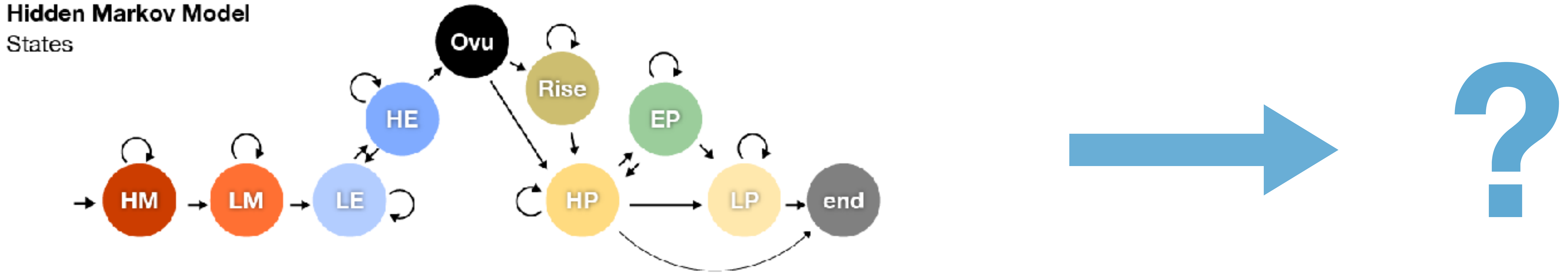


The distribution of durations spent in a given state is **geometric**.

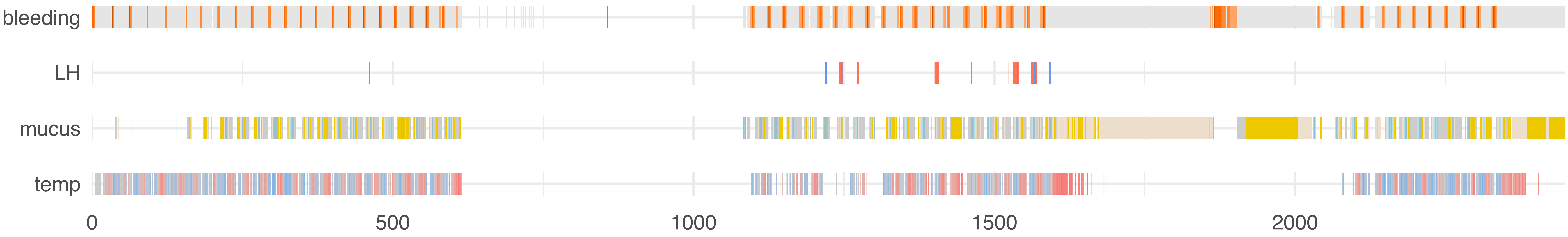
Hidden Semi-Markov Models (HSMM) are like HMM, but the **distribution of durations** spent in a state can be **specified as desired.**

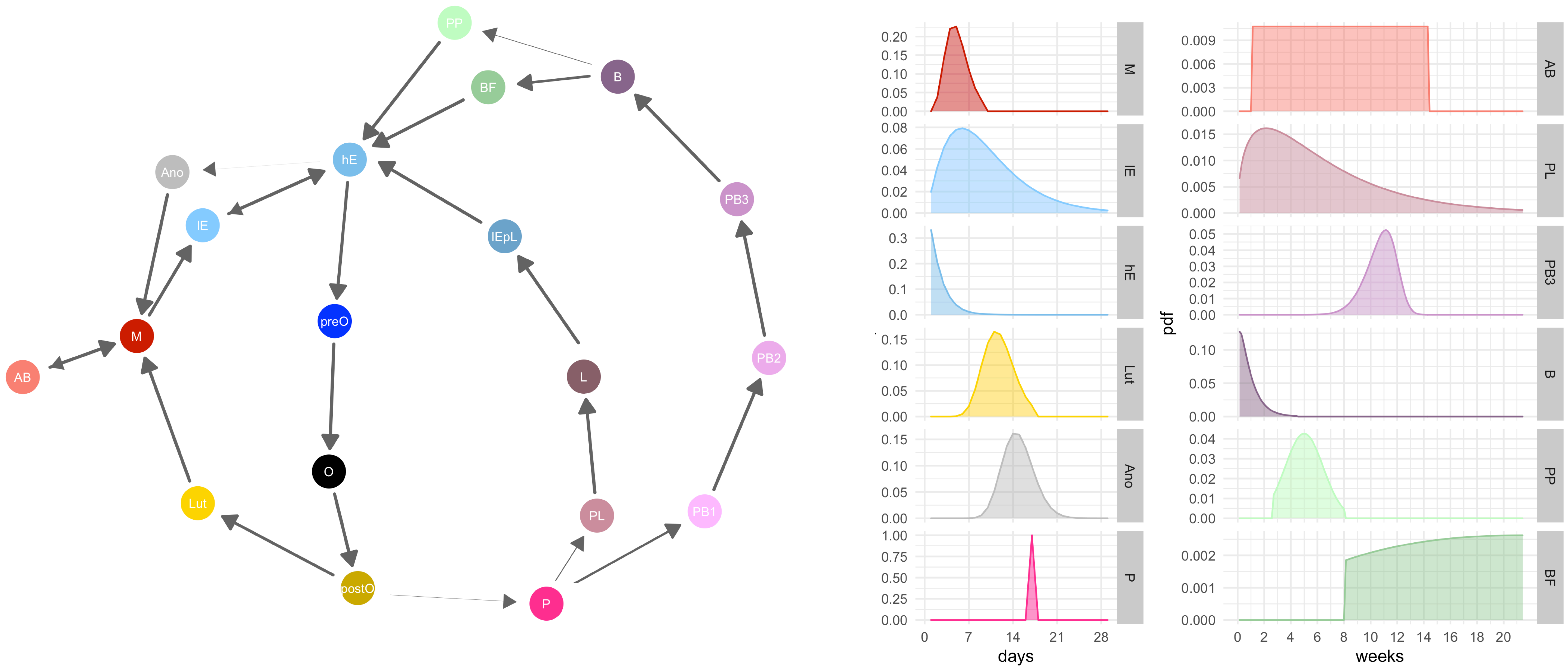






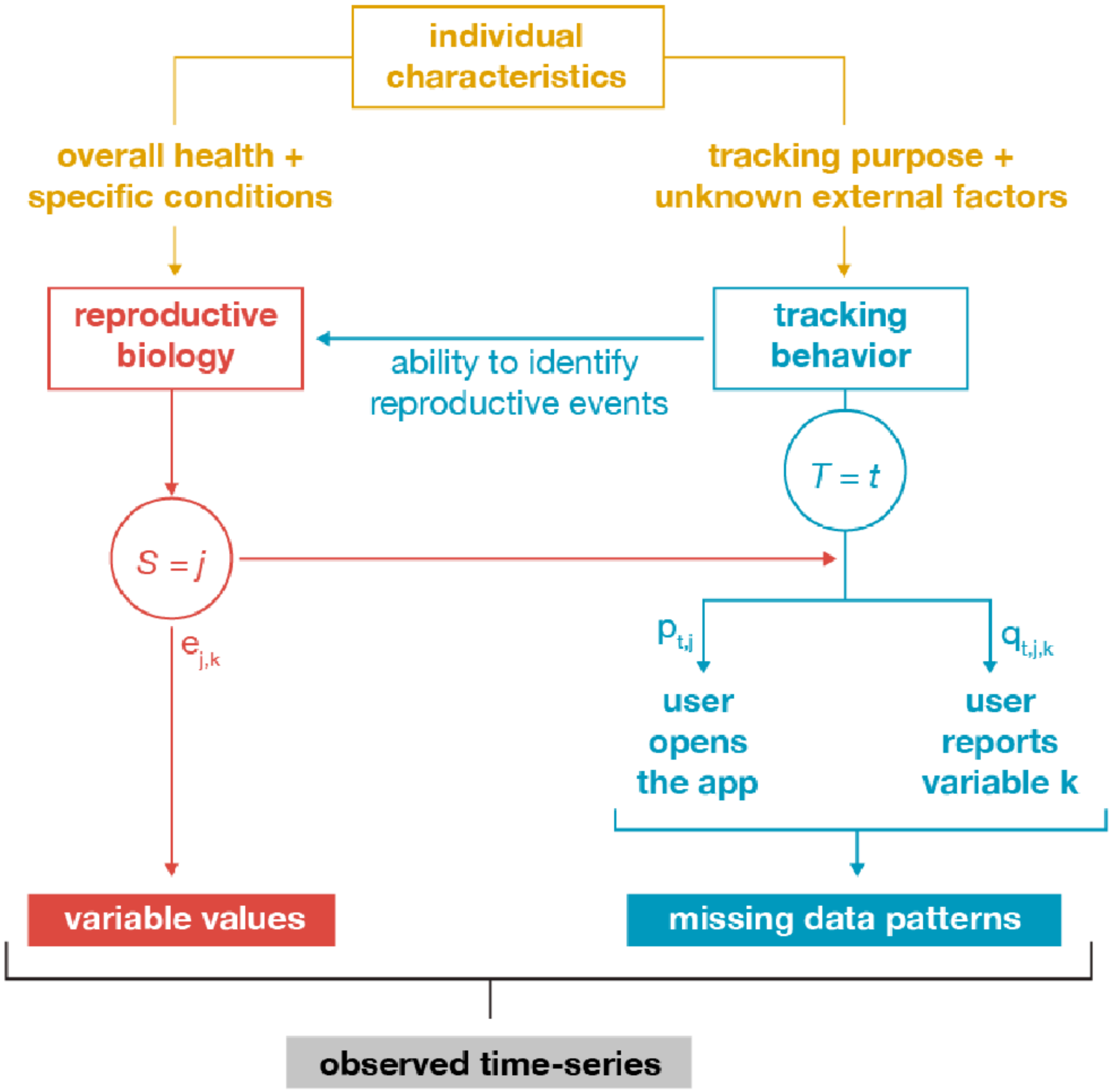
Now, how do we expand our menstrual cycles model to add pregnancies and prior knowledge on state duration with a HSMM?



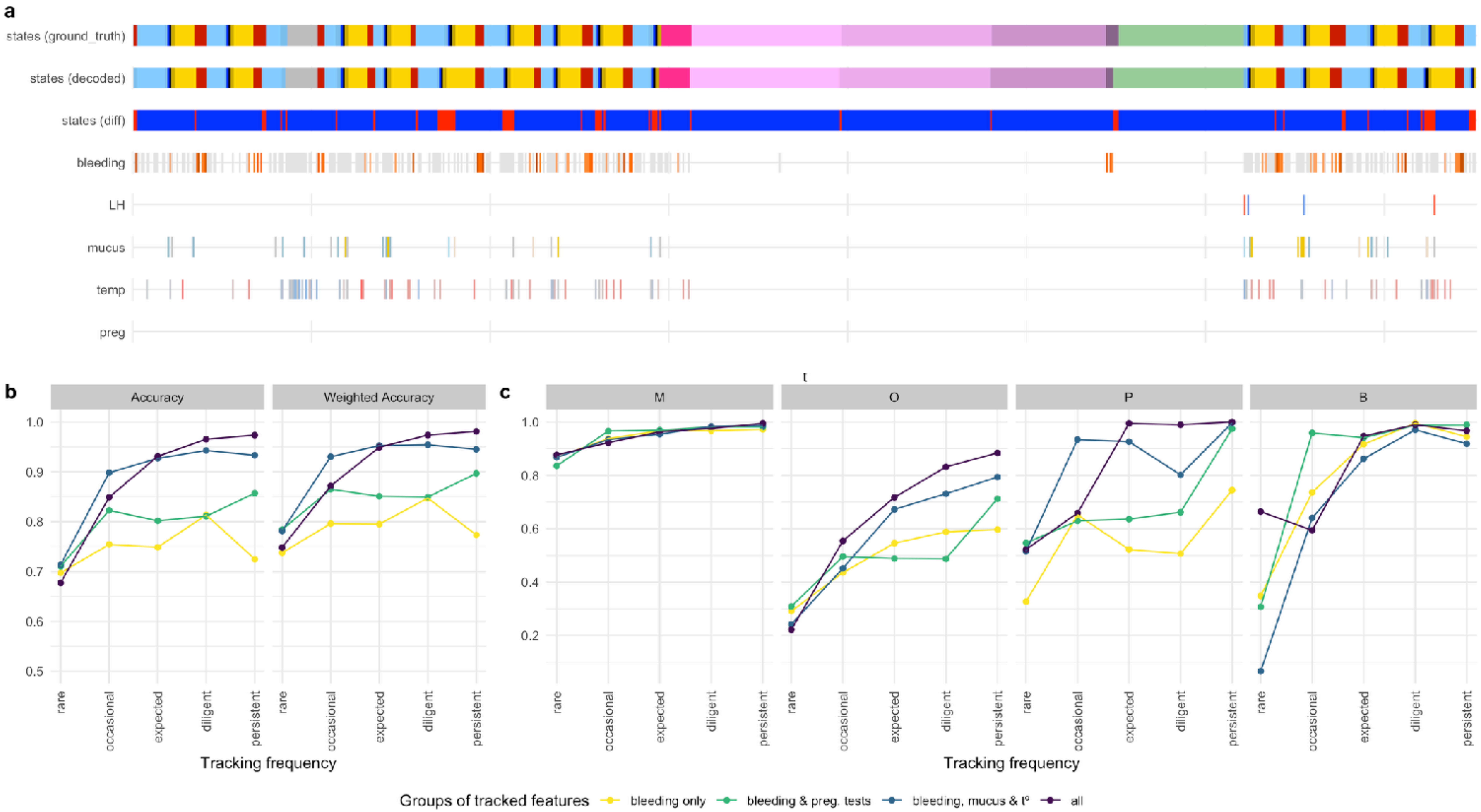


PP
B
BF
hE
Ano
lE
lEpL
PB3
M
preO
AB
L
PB2
O
Lut
PL
PB1
postO
P
M
lE
hE
Lut
Ano
P
AB
PL
PB3
B
PP
BF
pdf
days
weeks

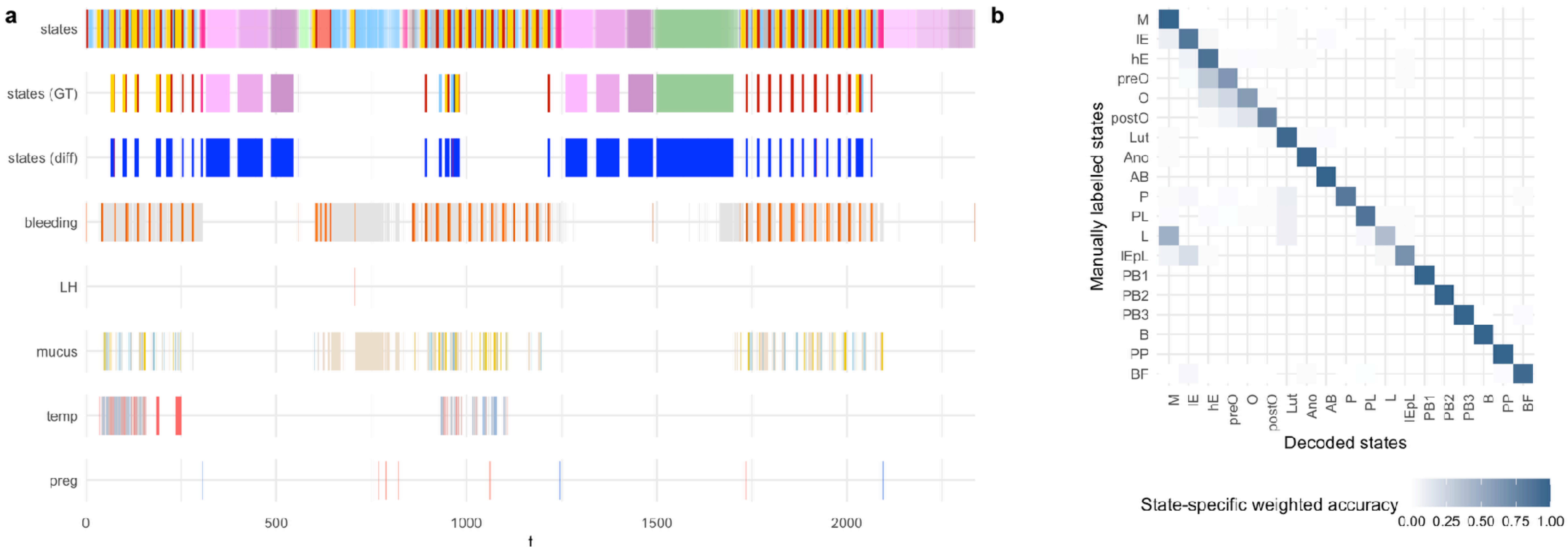
How do we adapt to changes in tracking behavior?



Since our model is a **generative model**, we can **simulate** some data and **control the amount of missingness** in our time-series (we can remove data points or variables all together).
We can then **evaluate our ability to recovered the simulated sequence of state** for varying amounts of missingness.



We then also manually labelled a small fraction of actual time-series (time series logged by the app users) and evaluated our performances on these labelled data.



Summary:

- **Birth seasonality** appears to be **mainly driven by seasonal fertility**.
  The **peak time** of fertility is **hemisphere-specific**.
- **Changes in sexual activity**, mainly **around holidays**, contribute to give the **location-specific fine-structure** of the birth curve
- It is unclear if changes in fertility are driven by **changes in female and/or male fertility.**

- **Users of fertility app report body-signs** patterns **consistent** with those reported in the medical literature
- When reported consistently, these body-signs can be used to **estimate the timing of ovulation** with **hidden Markov models**.
- The **distribution of estimated ovulation time is consistent** with the distribution previously reported.

- To further **label full time-series** and **identify events important to quantify fertility** (e.g. ovulation, pregnancies, pregnancy losses, etc.) we turned to **coupled hidden semi-Markov models**.
- The first model is a **model of the reproductive biology.**
- The second model is a **model of tracking behavior.**
- Together, **they reliably identify reproductive events.**
- The **next step** is to run these models on the full datasets to **quantify fertility metrics seasonally.**

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Menst. phases
Follicular phase
Luteal phase
Hormonal levels
day 1
LH
Ovulation
Progesterone
day 1
Estradiol
FSH
Inflammation
Ovarian cycle
Dominant follicle
Egg
Corpus luteum
Uterine cycle
Endometrium
Fertility-related body signs
Menstruation
Cervical mucus
Basal body temperature
~0.35C
Period
Fertile window
PMS/PME/PMDD
Period

What is PMS, PME or PMDD?

PMS: pre-menstrual syndrome
PME: pre-menstrual exacerbation
PMDD: pre-menstrual dysphoric disorder

PMDD* only is a **DSM-5** recognized mental health problem.
Its diagnosis **requires a 30% increase in symptoms** across at least 5 DSM5 domains during the 2 weeks preceding the menses with a complete clearance after the menses for at least 2 cycles.
Affects ~ 5-8% of the menstruating population.

PME is an exacerbation of symptoms during the pre-menstrual phase, without complete clearance after the menses. For example, someone who suffers of depression might have worst symptoms in the pre-menstrual phase.

PMS is a mild (to very mild) form of PMDD/PME. For example maybe only a few symptoms (like irritability or depression) increases by 30+% but not enough of them to “qualify” for PMDD diagnosis.
Or, they might all increase by only a small amount (like 10%).
May affect as much as 70% of the menstruating population.

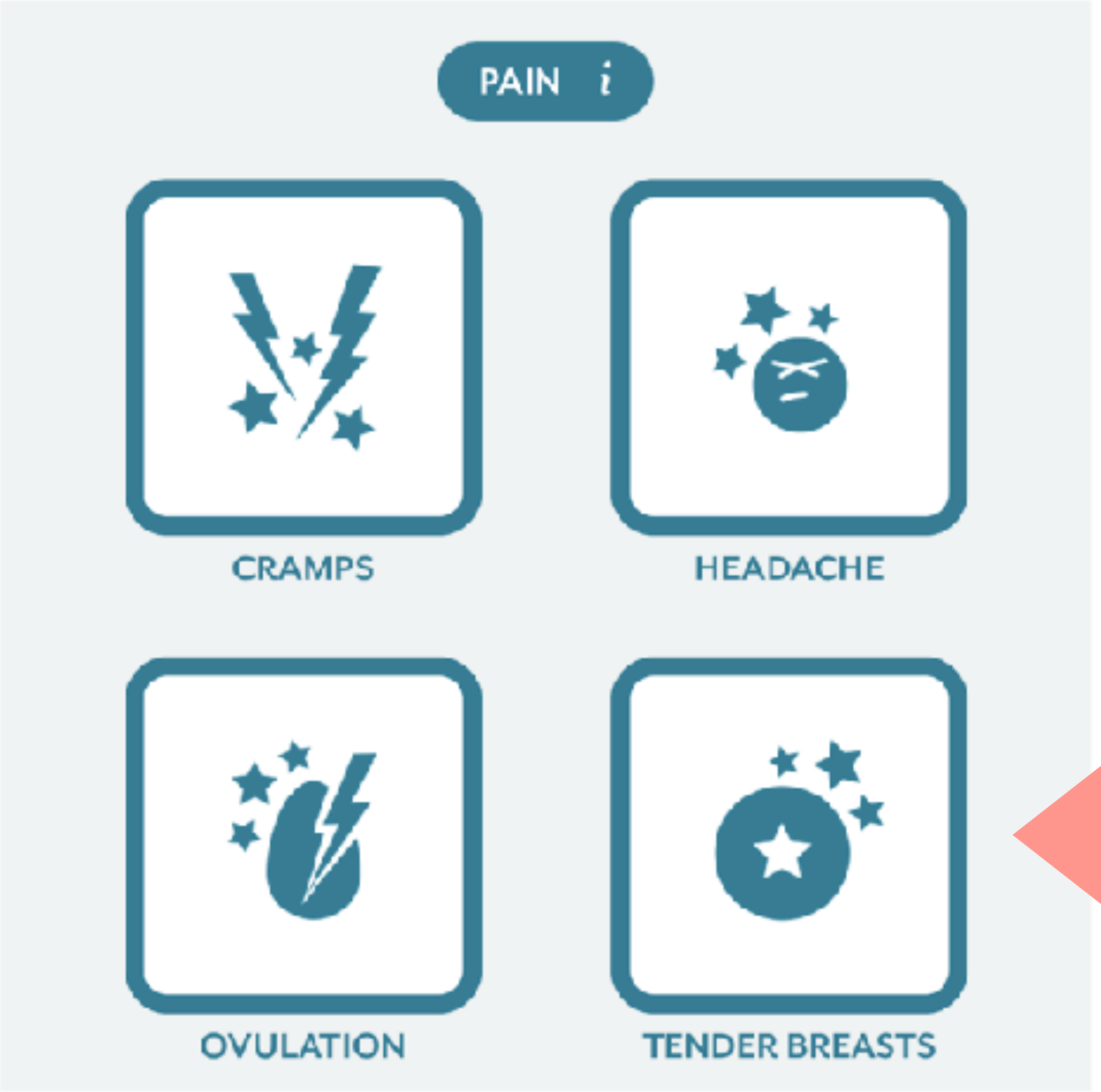
* if you think you have PMDD (premenstrual dysphoric disorder), don’t suffer alone, get help. The first step is to report symptoms for 2 cycles or more to refine the diagnosis. The next step is to get medication and/or get therapy to find coping mechanisms that work for you.

Most symptoms of PMDD are emotional symptoms, but there are also a few physical symptoms

PMS: pre-menstrual syndrome
PME: pre-menstrual exacerbation
PMDD: pre-menstrual dysphoric disorder

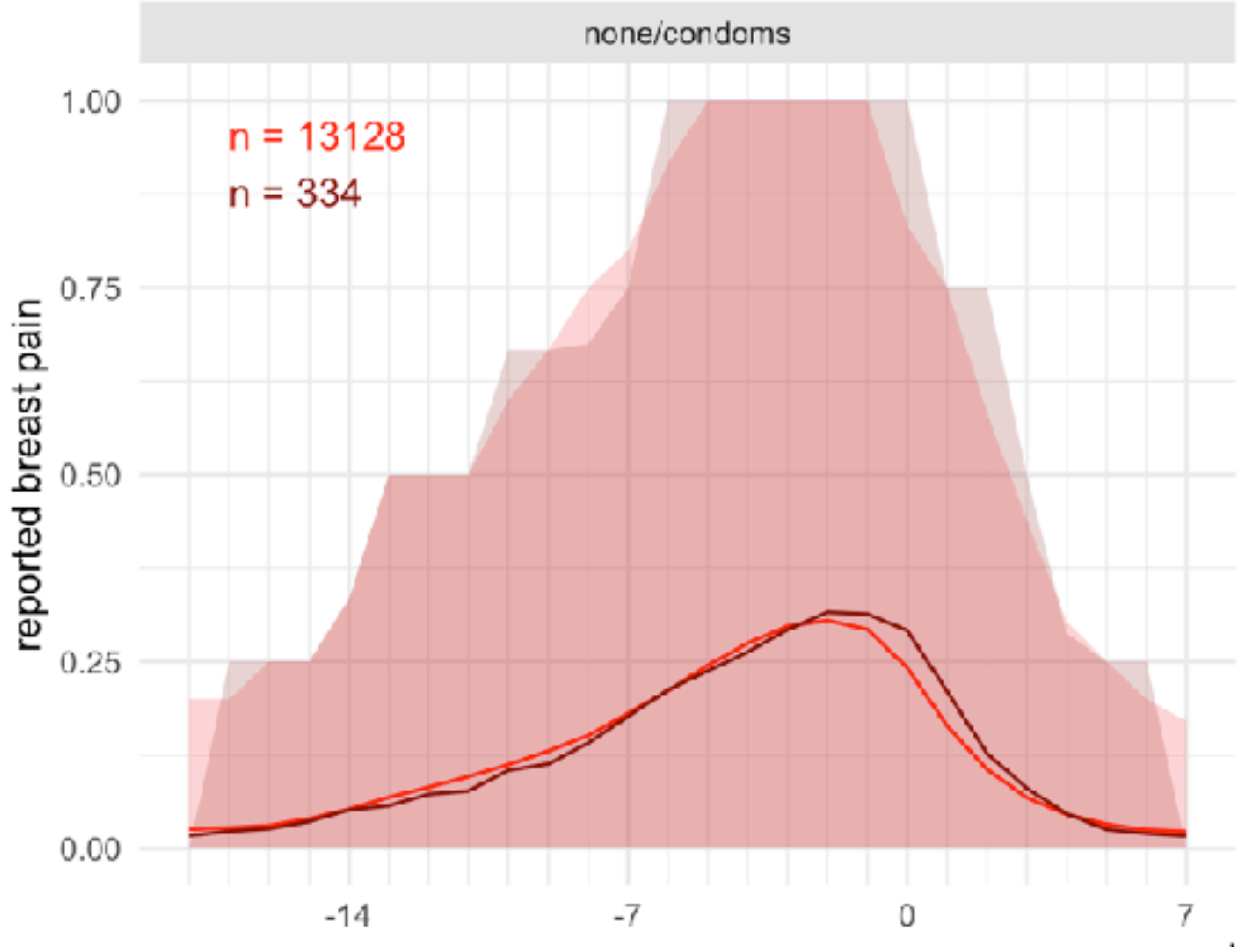
Is the timing of symptoms the same for everyone?

To answer this question, we turn to the Clue data again:

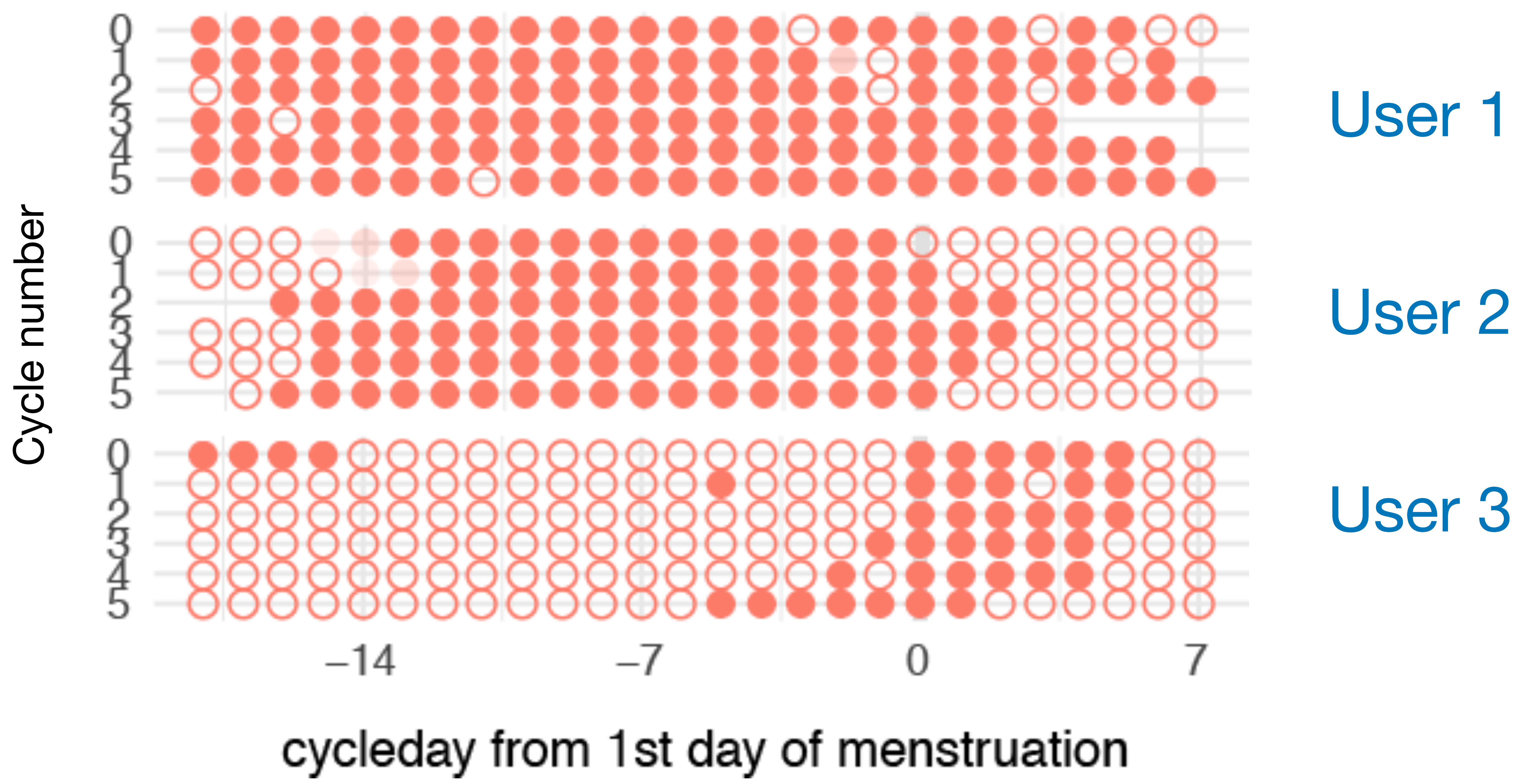


And focus on the breast pain symptom

The average breast pain profile is very pre-menstrual



But digging into the individuals profiles, we find that some users have very specific and consistent symptom temporal patterns



Future research is needed to correlate these temporal patterns with biological biomarkers.

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References

1. Symul L, Hsieh P, Shea A, Skene DJ, Holmes S, Martinez M. Unmasking Seasonal Cycles in Human Fertility: How holiday sex and fertility cycles shape birth seasonality. MedRxiv 2020.
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3. Symul L, Wac K, Hillard P, Salathé M. Assessment of Menstrual Health Status and Evolution through Mobile Apps for Fertility Awareness. npj Digital Medicine 2019.

Thank you

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