

Statistical learning on period app data to advance personalized health care for women

AMLD2020 Laura Symul

@LauraSymul lsymul@stanford.edu



Women* menstruate

The menstrual cycle is crucial for reproduction

The menstrual cycle is crucial for reproduction

Because of its crucial role for the survival of the species, it should not surprise anyone that the menstrual cycle has far-reaching effects on our health, behaviors and emotional states, beyond its reproductive dimension and that the hormonal regulation pathways are redundant, robust and complex.

The menstrual cycle is crucial for reproduction

Because of its crucial role for the survival of the species, it should not surprise anyone that the menstrual cycle has far-reaching effects on our health, behaviors and emotional states, beyond its reproductive dimension and that the hormonal regulation pathways are redundant, robust and complex.

There are active estrogen receptors in virtually every tissue of the human body

The menstrual cycle has long been an

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect),

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example)

The menstrual cycle has long been an
Understudied (mostly focusing on the fertility aspect),
Under-funded (so little money to study endometriosis for example)
& quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective)

The menstrual cycle has long been an
Understudied (mostly focusing on the fertility aspect),
Under-funded (so little money to study endometriosis for example)
& quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective)
field of research

The menstrual cycle has long been an
Understudied (mostly focusing on the fertility aspect),
Under-funded (so little money to study endometriosis for example)
& quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective)
field of research

The menstrual cycle has long been an
Understudied (mostly focusing on the fertility aspect),
Under-funded (so little money to study endometriosis for example)
& quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective)
field of research

We still do not know...

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?
 - An evolutionary strategy to lead infertile couples to break-ups?

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?
 - An evolutionary strategy to lead infertile couples to break-ups?
- The drivers of human birth seasonality? Which aspects of fertility are seasonal?

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?
 - An evolutionary strategy to lead infertile couples to break-ups?
- The drivers of human birth seasonality? Which aspects of fertility are seasonal?
- How menstrual bleeding is regulated

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?
 - An evolutionary strategy to lead infertile couples to break-ups?
- The drivers of human birth seasonality? Which aspects of fertility are seasonal?
- How menstrual bleeding is regulated
 - and, consequently what happens during anovulatory cycles?

The menstrual cycle has long been an Understudied (mostly focusing on the fertility aspect), Under-funded (so little money to study endometriosis for example) & quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective) field of research

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?
 - An evolutionary strategy to lead infertile couples to break-ups?
- The drivers of human birth seasonality? Which aspects of fertility are seasonal?
- How menstrual bleeding is regulated
 - and, consequently what happens during anovulatory cycles?
- What drives irregularity in menstrual cycles in the absence of medical conditions and why a specific cycle is longer or shorter.

The menstrual cycle has long been an

Understudied (mostly focusing on the fertility aspect),

Under-funded (so little money to study endometriosis for example)

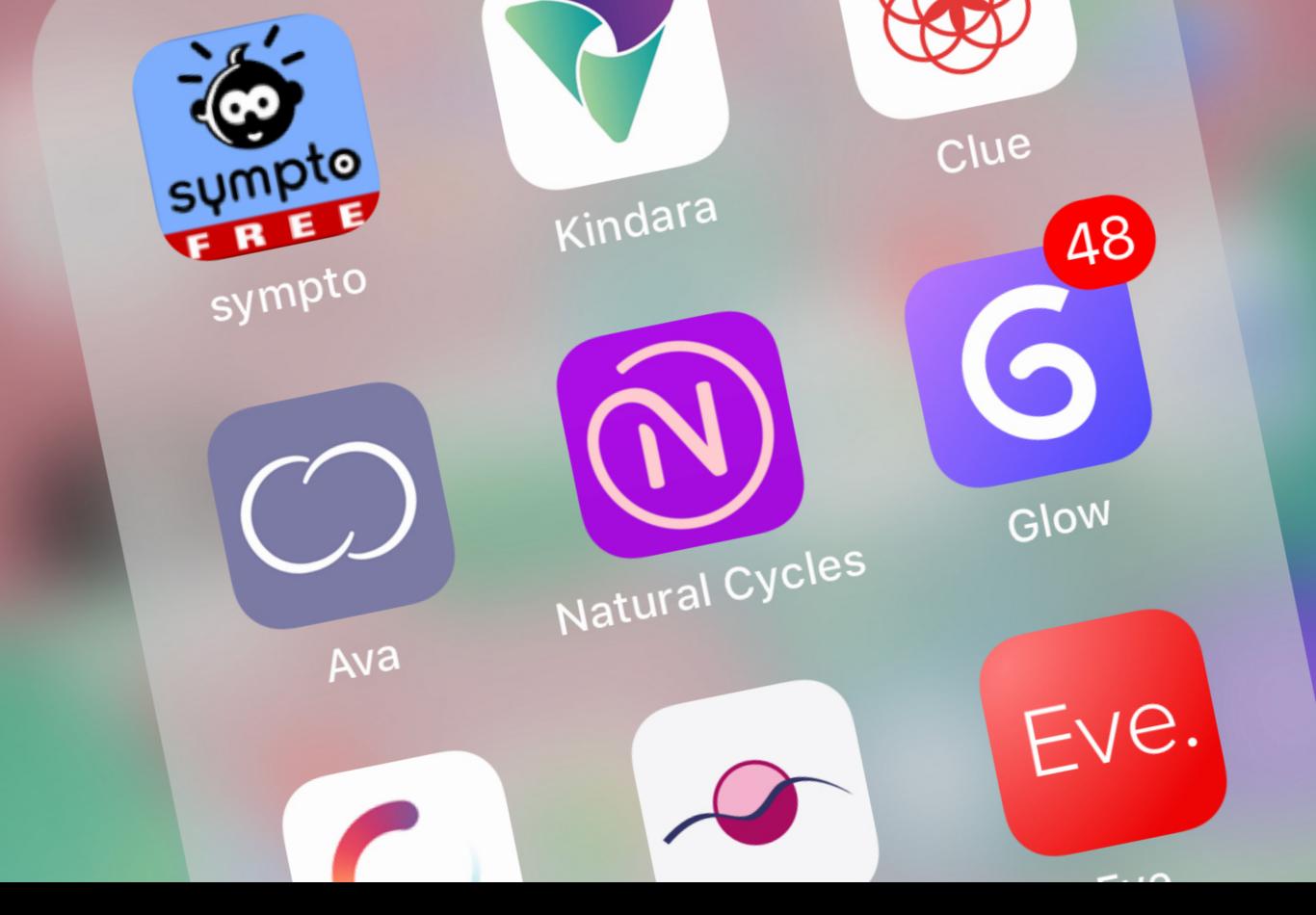
& quasi mono-disciplinary (mostly research by obstetricians & gynecologists, where the circadian clock, another fundamental biological rhythm, has been heavily studied from a medical, biological, ecological, modeling perspective)

field of research

We still do not know...

- The causes of pre-menstrual symptoms and pre-menstrual dysphoric disorder
 - A genetic predisposition?
 - An hormonal sensitivity? General? Tissue-specific?
 - An abnormality of the immune system? In the interactions with the immune system?
 - An evolutionary strategy to lead infertile couples to break-ups?
- The drivers of human birth seasonality? Which aspects of fertility are seasonal?
- How menstrual bleeding is regulated
 - and, consequently what happens during anovulatory cycles?
- What drives irregularity in menstrual cycles in the absence of medical conditions and why a specific cycle is longer or shorter.

Data?



Millions of women now use apps & wearables to track their cycle

Long term tracking



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



Deep Learning

Human-like Learning

Deep Learning

Human-like Learning

A TON of labeled examples

Dogs

































































































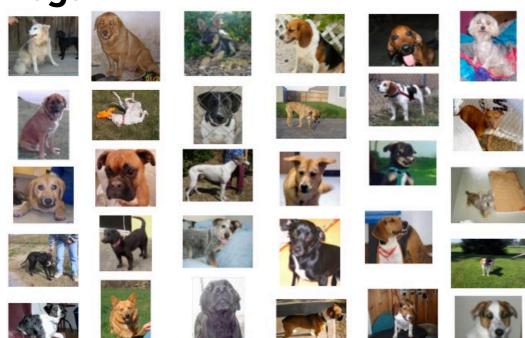




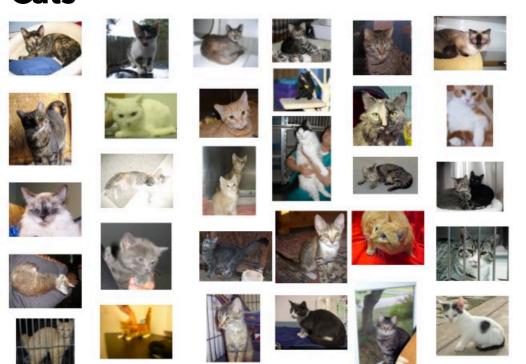
Deep Learning

A TON of labeled examples

Dogs



Cats



Human-like Learning

Facts, contrasting information

Deep Learning

A TON of labeled examples

Dogs





























































































Facts, contrasting information

Dogs

- 4 legged animals (mammals)
- Size: from ~20 cm to ~1m (large diversity in sizes)
- Hair type: short hair, long hair or fluffy curly hair
- Hair Color: mostly shades of brown, but also white or black
- Most dogs have long nose with black truffle
- Ears: mostly falling on the side of head, except when paying attention to smth

Deep Learning

A TON of labeled examples

Dogs











































































Human-like Learning

Facts, contrasting information

Dogs

- 4 legged animals (mammals)
- Size: from ~20 cm to ~1m (large diversity in sizes)
- Hair type: short hair, long hair or fluffy curly hair
- Hair Color: mostly shades of brown, but also white or black
- Most dogs have long nose with black truffle
- Ears: mostly falling on the side of head, except when paying attention to smth

Cats

- 4 legged animals (mammals)
- Size: 25cm ± 5cm (smaller variance in size than dogs)
- Hair type: mostly short hair, sometimes long, can be fluffy (but not curly)
- Hair Color: white, black, gray, warm brown. "Tigger pattern"
- Most cats have round faces with short noses
- Ears are pointy and mostly straight up.

Deep Learning

A TON of labeled examples

Dogs

































Cats































Facts, contrasting information

Dogs

- 4 legged animals (mammals)
- Size: from ~20 cm to ~1m (large diversity in sizes)
- Hair type: short hair, long hair or fluffy curly hair
- Hair Color: mostly shades of brown, but also white or black
- Most dogs have long nose with black truffle
- Ears: mostly falling on the side of head, except when paying attention to smth

Cats

- 4 legged animals (mammals)
- Size: 25cm ± 5cm (smaller variance in size than dogs)
- Hair type: mostly short hair, sometimes long, can be fluffy (but not curly)
- Hair Color: white, black, gray, warm brown. "Tigger pattern"
- Most cats have round faces with short noses
- Ears are pointy and mostly straight up.

A few examples





Deep Learning

A TON of labeled examples

Dogs





































































or Model-based Stat L

Facts, contrasting information

Dogs

- 4 legged animals (mammals)
- Size: from ~20 cm to ~1m (large diversity in sizes)
- Hair type: short hair, long hair or fluffy curly hair
- Hair Color: mostly shades of brown, but also white or black
- Most dogs have long nose with black truffle
- Ears: mostly falling on the side of head, except when paying attention to smth

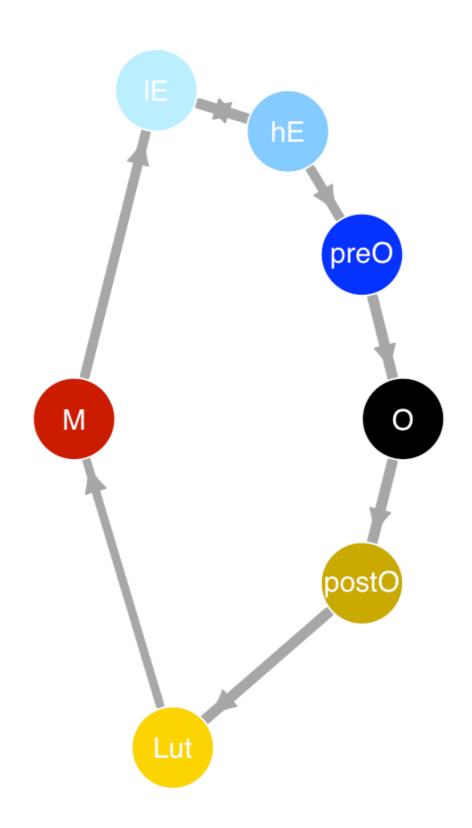
Cats

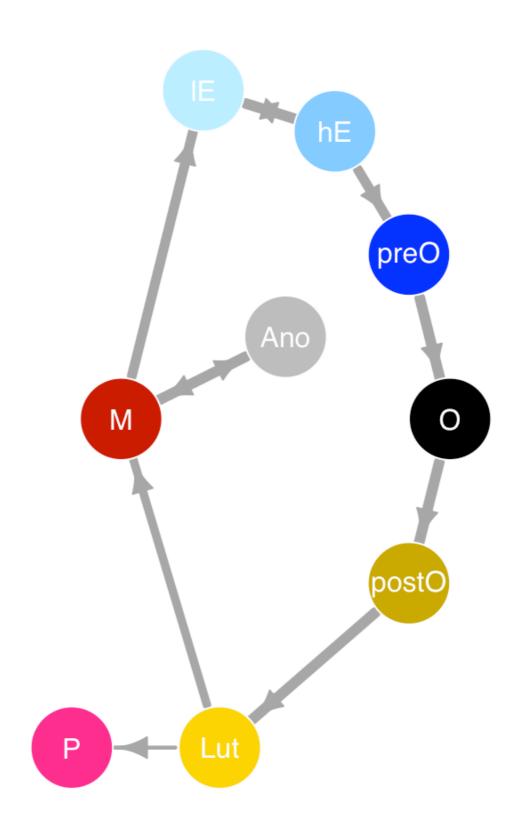
- 4 legged animals (mammals)
- Size: 25cm ± 5cm (smaller variance in size than dogs)
- Hair type: mostly short hair, sometimes long, can be fluffy (but not curly)
- Hair Color: white, black, gray, warm brown. "Tigger pattern"
- Most cats have round faces with short noses
- Ears are pointy and mostly straight up.

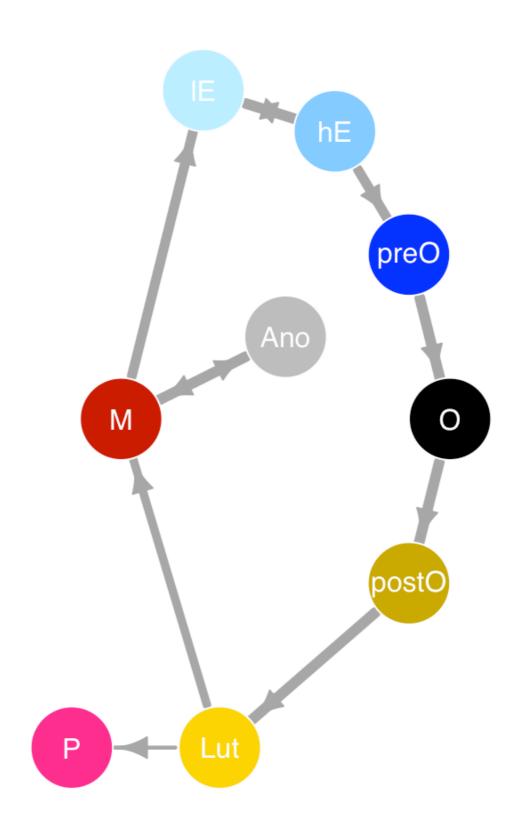
A few examples

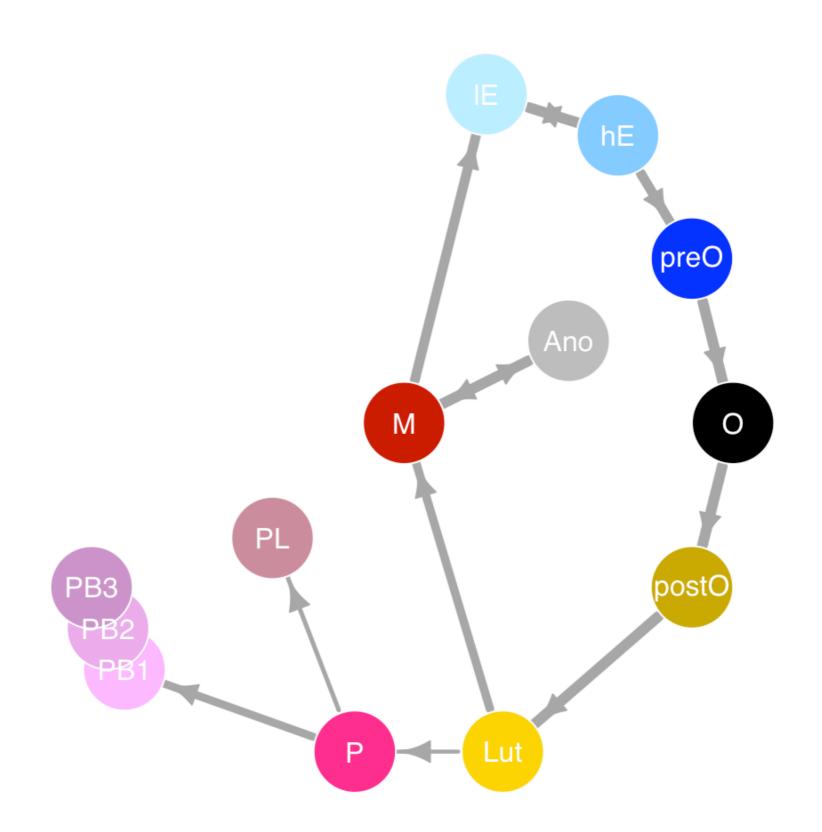


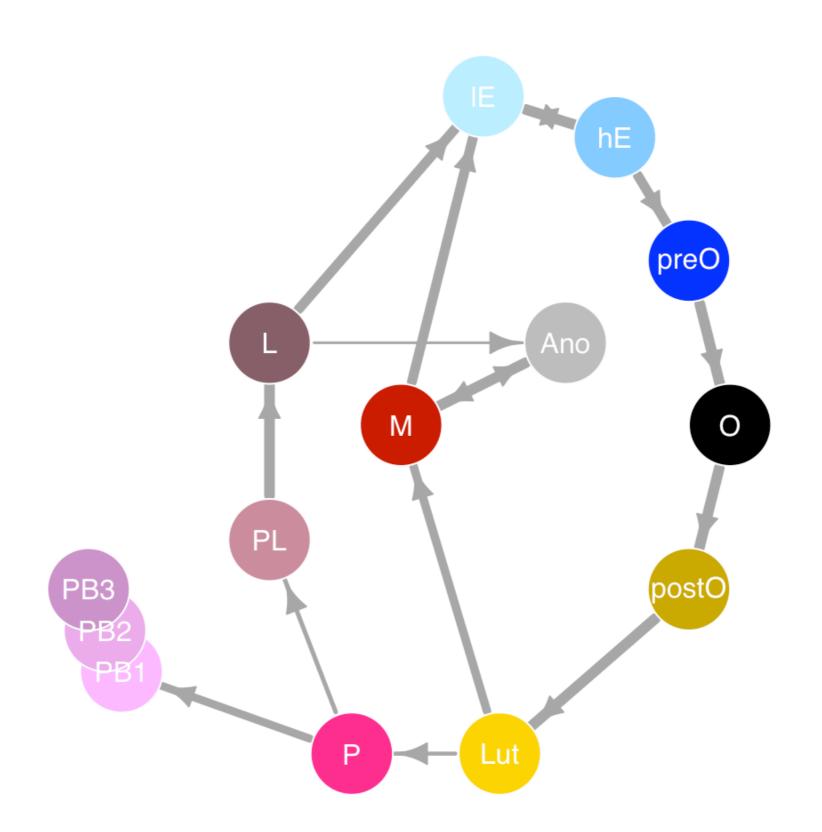


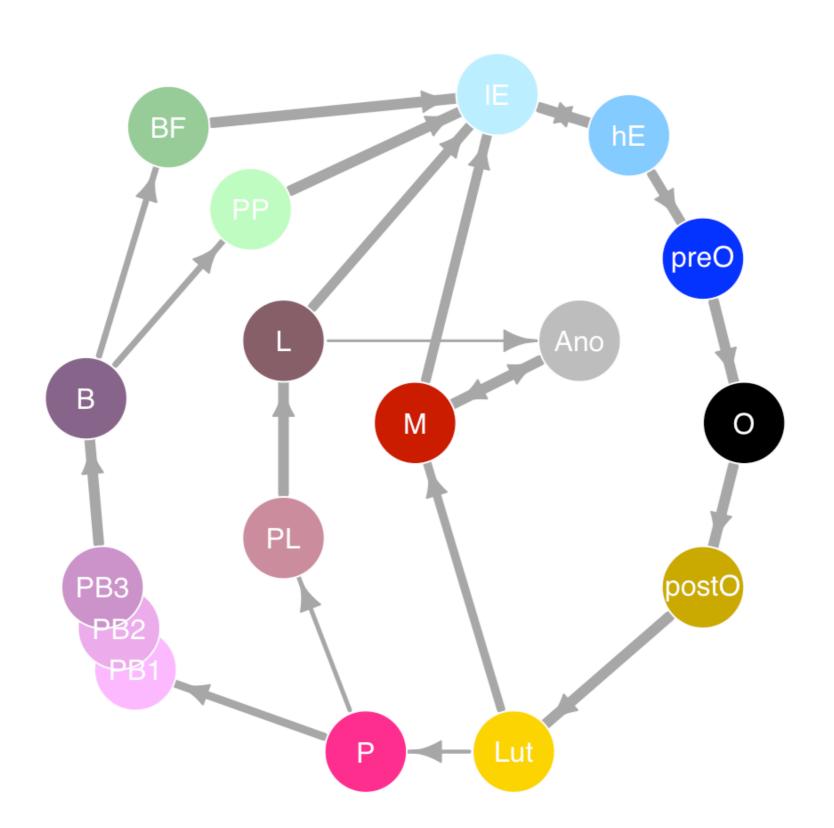


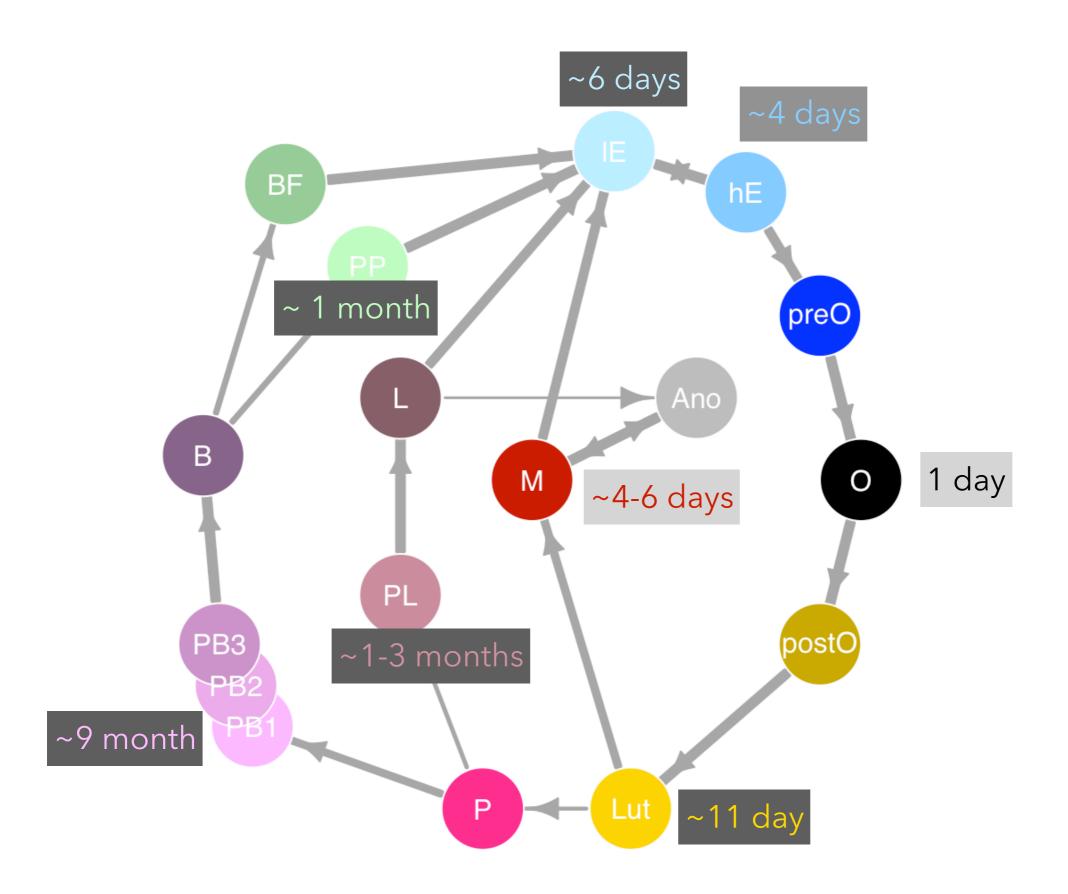


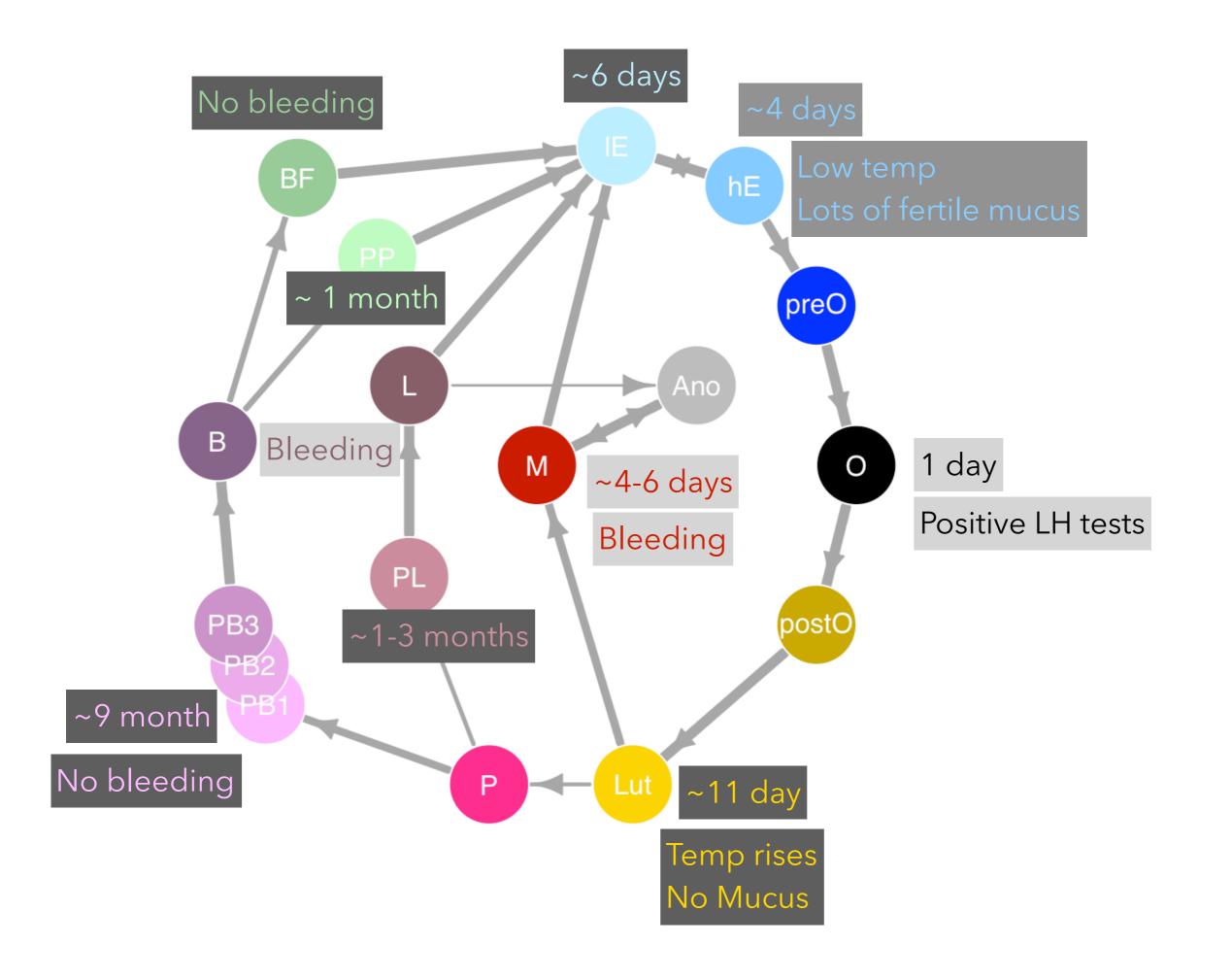


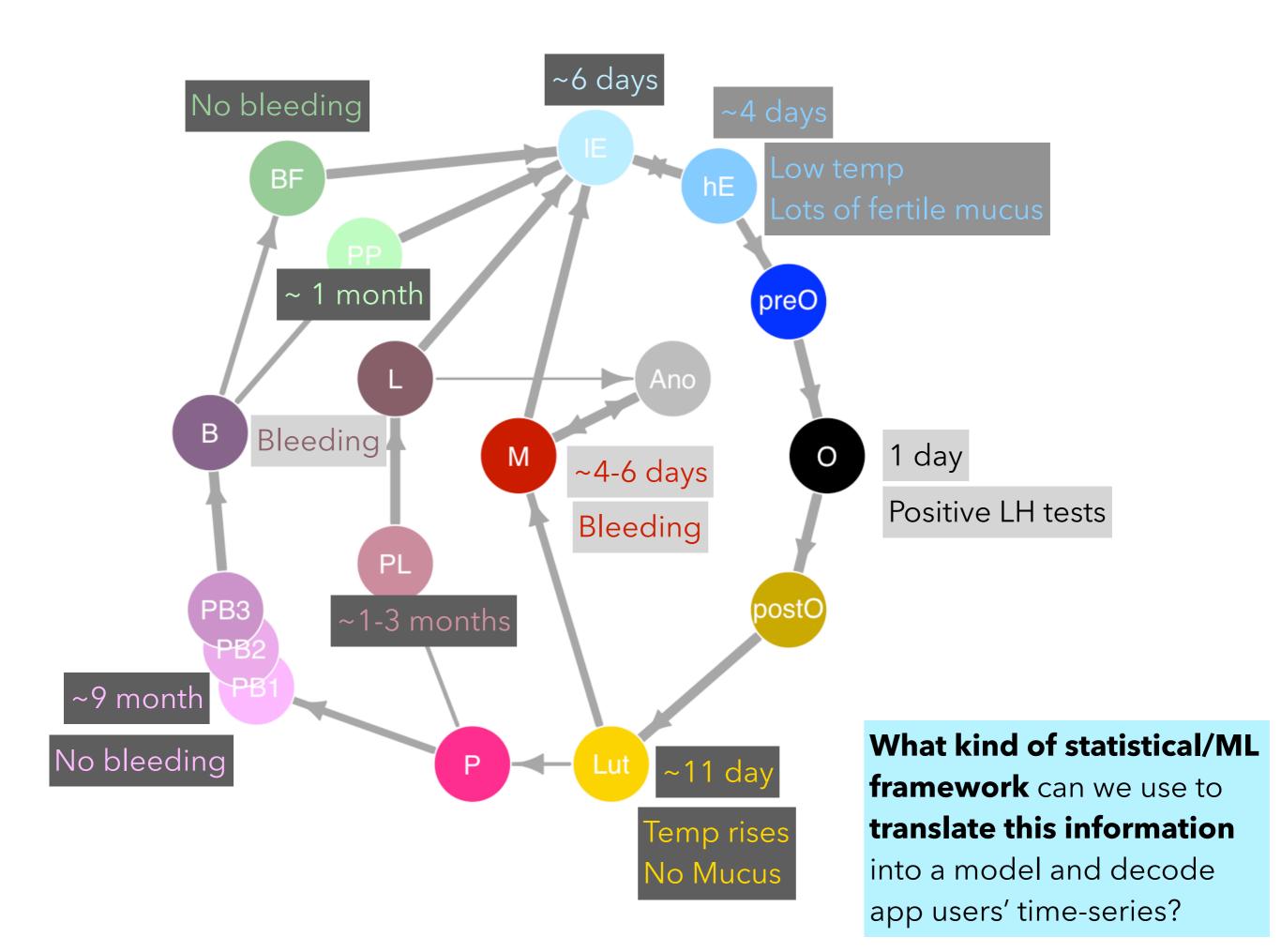


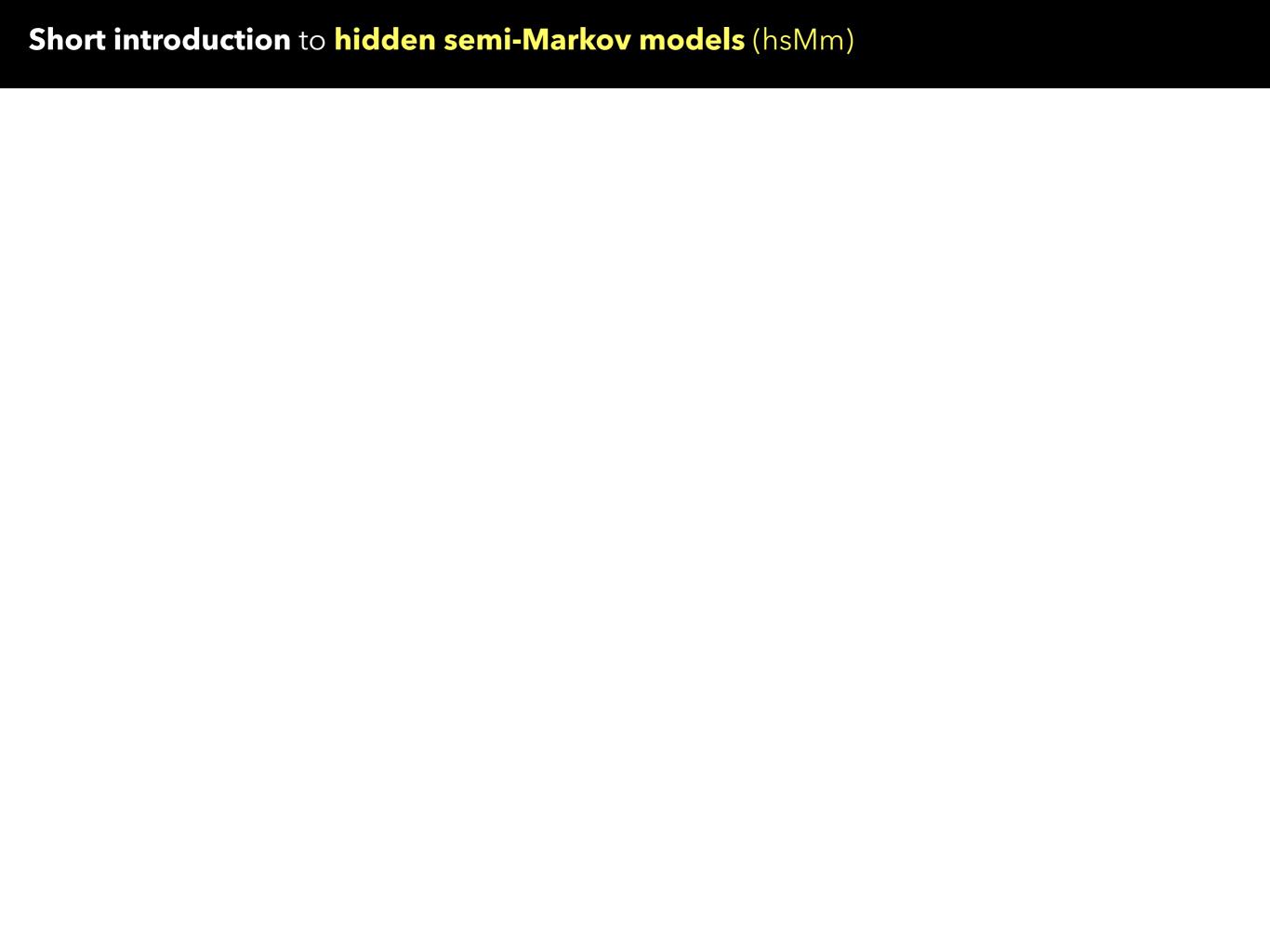












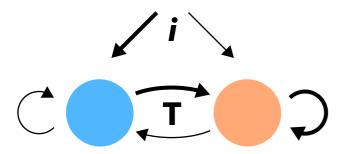






- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

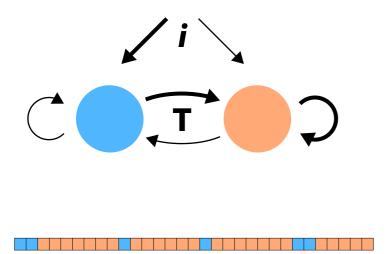
Hidden Markov Models



- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

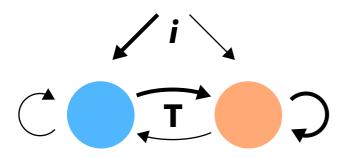
- **Initial state** probability vector

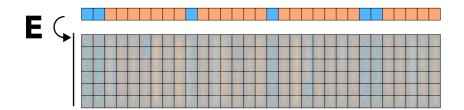
Hidden Markov Models



- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

- **Initial state** probability vector

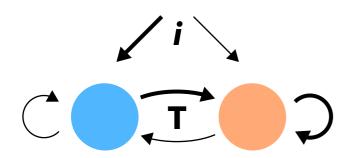


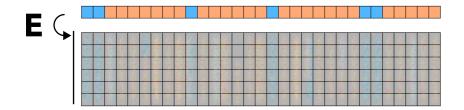


- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

- **Initial state** probability vector
- **Emission probabilities** for the observed variables

Hidden Markov Models



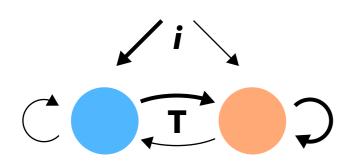


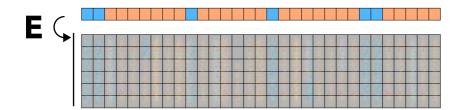
- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

- **Initial state** probability vector
- **Emission probabilities** for the observed variables

Hidden semi-Markov Models

Hidden Markov Models

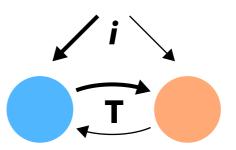




- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

- **Initial state** probability vector
- **Emission probabilities** for the observed variables

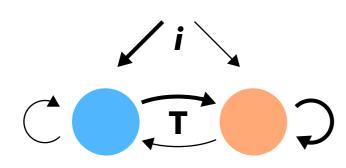
Hidden semi-Markov Models

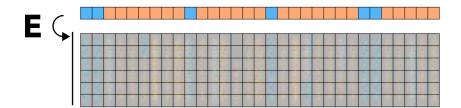


- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

- **Initial state** probability vector

Hidden Markov Models

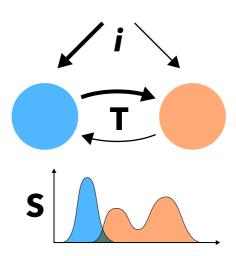




- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

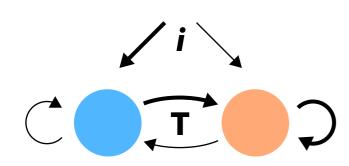
- **Initial state** probability vector
- **Emission probabilities** for the observed variables

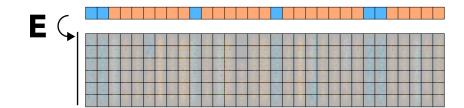
Hidden semi-Markov Models



- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state
- **Sojourn** distributions: the time spent in a given state
- **Initial state** probability vector

Hidden Markov Models

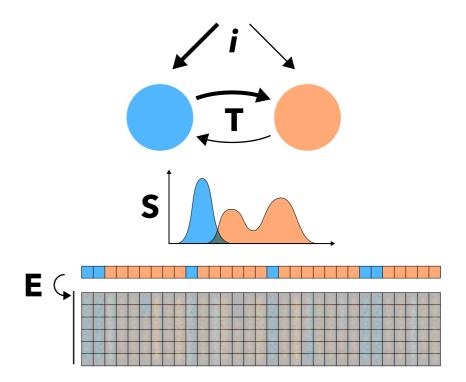




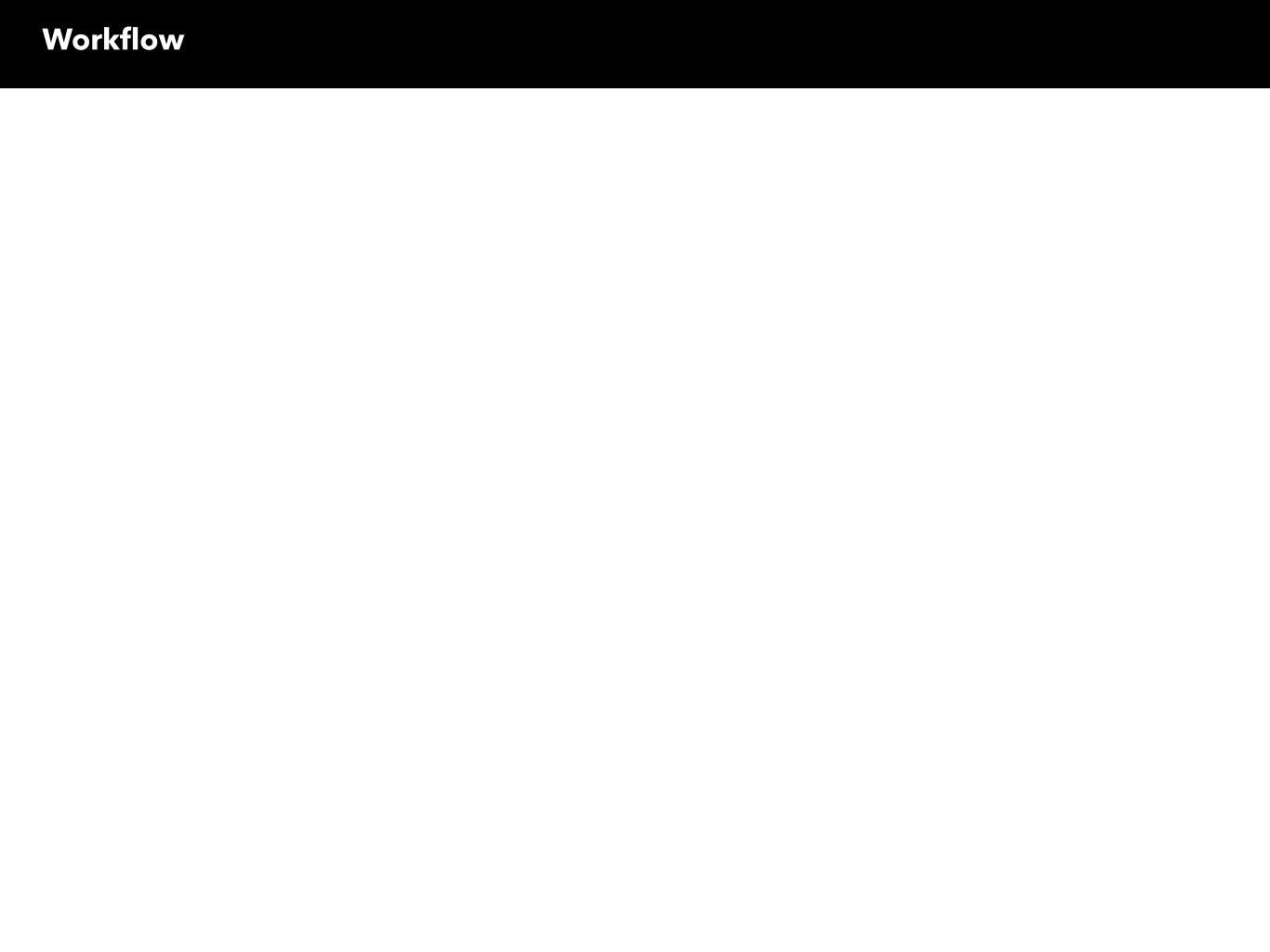
- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state

- **Initial state** probability vector
- **Emission probabilities** for the observed variables

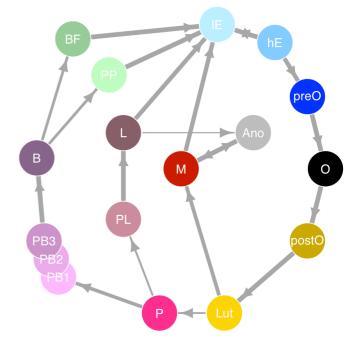
Hidden semi-Markov Models



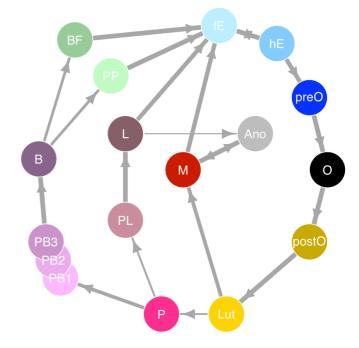
- **Transition** probabilities (matrix)
 - To switch states
 - To stay in same state
- **Sojourn** distributions: the time spent in a given state
- **Initial state** probability vector
- Emission probabilities for the observed variables



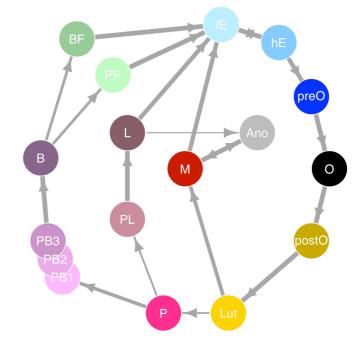
- Initialize the model architecture
 - ▶ The transition probabilities
 - ▶ The sojourn distributions
 - ▶ The emission probabilities



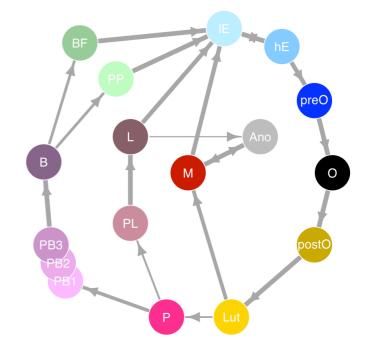
- Initialize the model architecture
 - ▶ The transition probabilities
 - ▶ The sojourn distributions
 - ▶ The emission probabilities
- Manually label a few time-series [R shiny app]



- Initialize the model architecture
 - ▶ The transition probabilities
 - ▶ The sojourn distributions
 - ▶ The emission probabilities
- Manually label a few time-series [R shiny app]
- Fit the model (EM approach)
 & decode the time-series with the fitted model
- Evaluate the accuracy (using the labelled t-s)
 & confidence (parametric bootstrap approach)
 in the decoded sequence
- [R shiny app] Manually label more time-series (where the decoding is wrong)
 & validate the decoding (where it got it right)

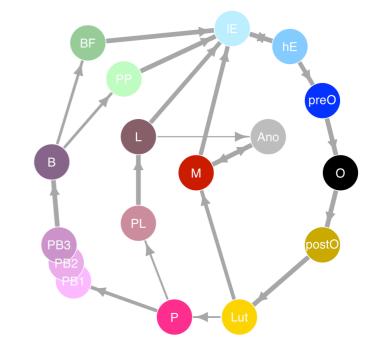


- Initialize the model architecture
 - ▶ The transition probabilities
 - ▶ The sojourn distributions
 - The emission probabilities
- Manually label a few time-series [R shiny app]
- Fit the model (EM approach)
 & decode the time-series with the fitted model
- Evaluate the accuracy (using the labelled t-s)
 & confidence (parametric bootstrap approach)
 in the decoded sequence
- [R shiny app] Manually label more time-series (where the decoding is wrong)
 & validate the decoding (where it got it right)





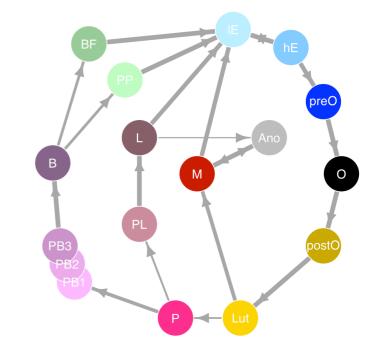
- Initialize the model architecture
 - ▶ The transition probabilities
 - ▶ The sojourn distributions
 - ▶ The emission probabilities
- Manually label a few time-series [R shiny app]
- Fit the model (EM approach)
 & decode the time-series with the fitted model
- Evaluate the accuracy (using the labelled t-s)
 & confidence (parametric bootstrap approach)
 in the decoded sequence
- [R shiny app] Manually label more time-series (where the decoding is wrong)
 & validate the decoding (where it got it right)





Decode all user's time-series

- Initialize the model architecture
 - ▶ The transition probabilities
 - ▶ The sojourn distributions
 - ▶ The emission probabilities
- Manually label a few time-series [R shiny app]
- Fit the model (EM approach)
 & decode the time-series with the fitted model
- Evaluate the accuracy (using the labelled t-s)
 & confidence (parametric bootstrap approach)
 in the decoded sequence
- [R shiny app] Manually label more time-series (where the decoding is wrong)
 & validate the decoding (where it got it right)

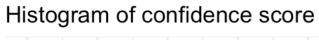




Decode all user's time-series

Epidemiological studies

Confidence in the decoded sequences





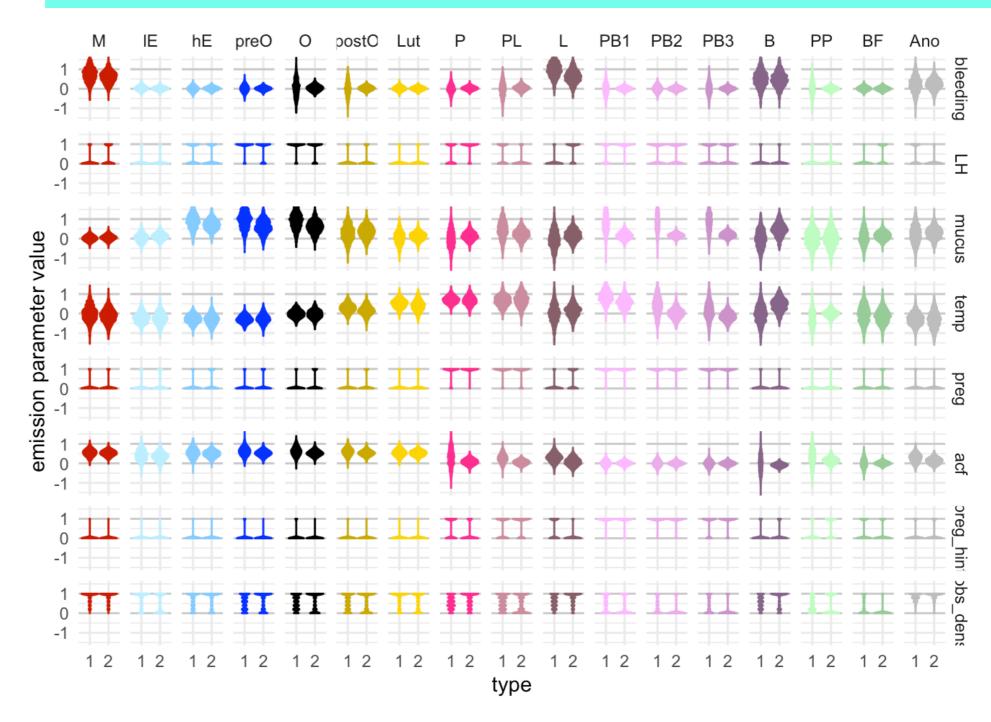
FALSE

TRUE

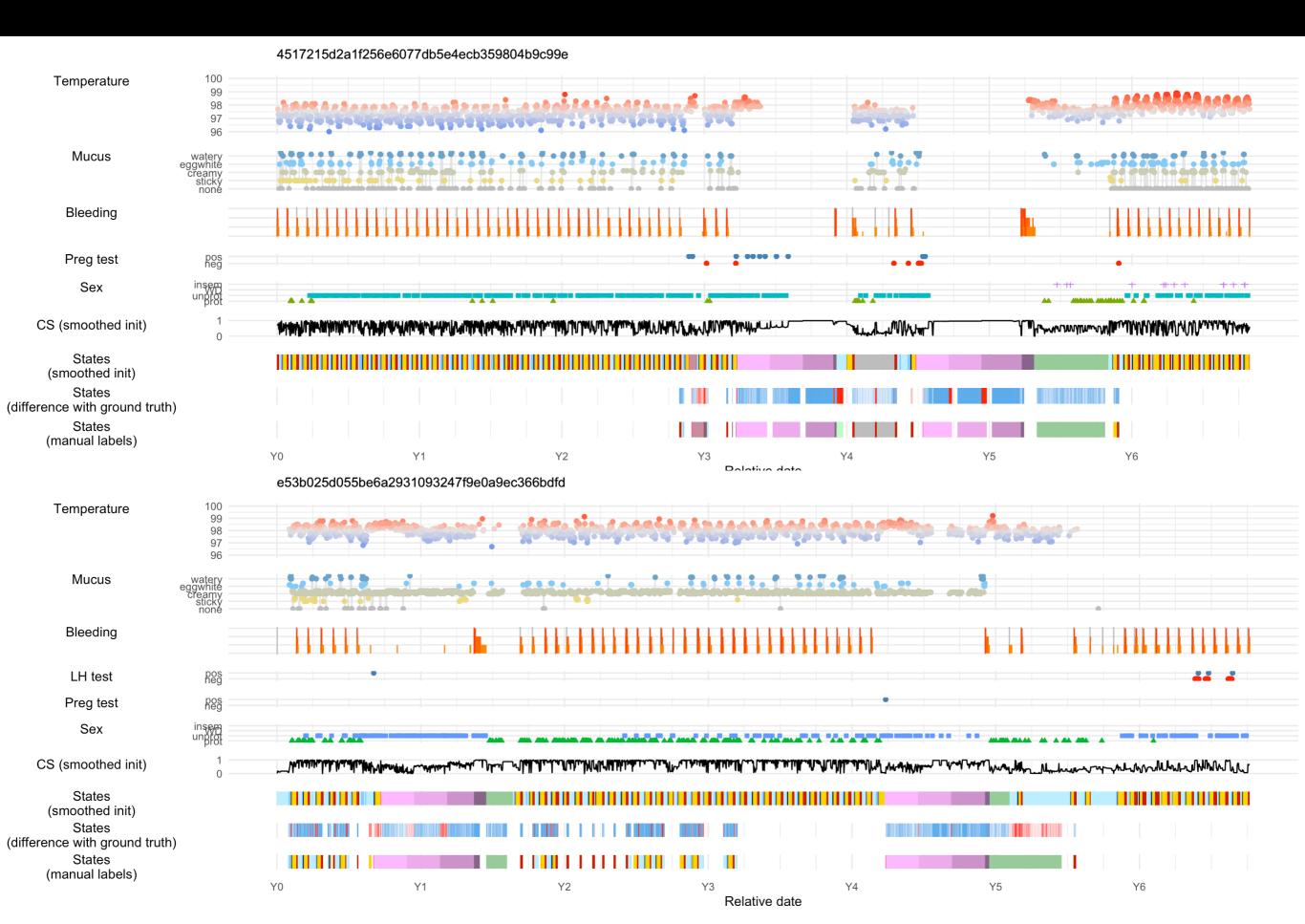
Accuracy ~80%

correct_decoding

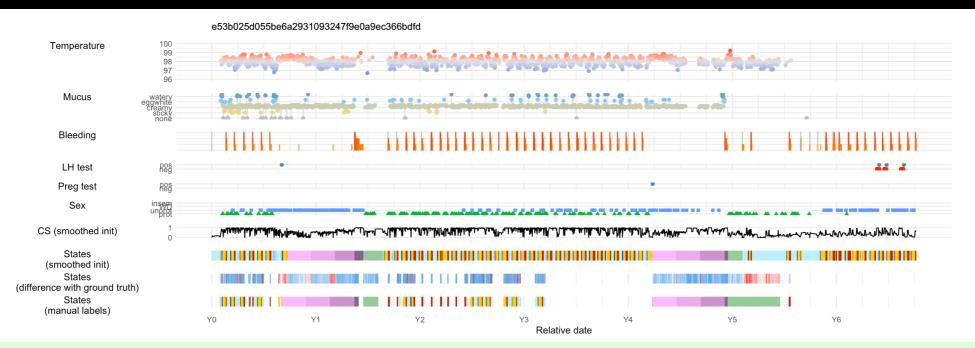
Emission parameters



Results



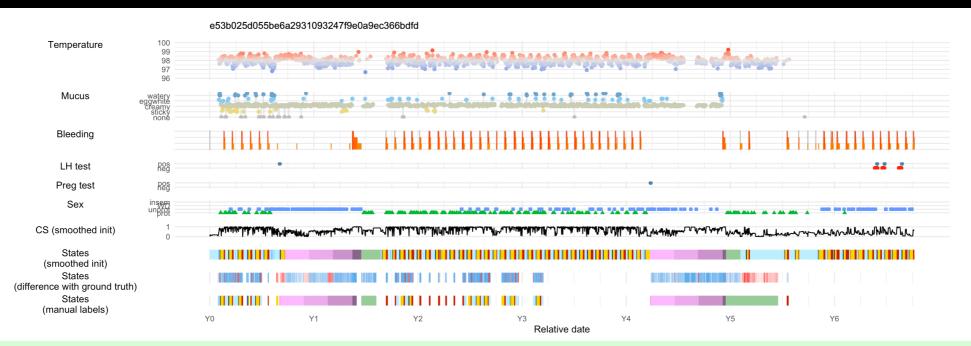
Conclusions



Upgraded 'hsmm' R package that

- can deal with high level of data missingness (as found in any digital health project)
- allows for any parametric or non-parametric distribution for the observed variables
 - which allow for discrete, categorical or continuous variables
- can quantify uncertainty by providing a confidence score for the decoded sequence, based on parametric bootstrap, independent of whether labelled data are available
- Available on my GitHub: @lasy

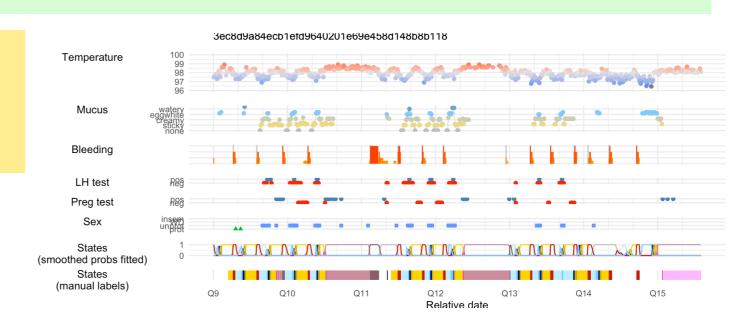
Conclusions



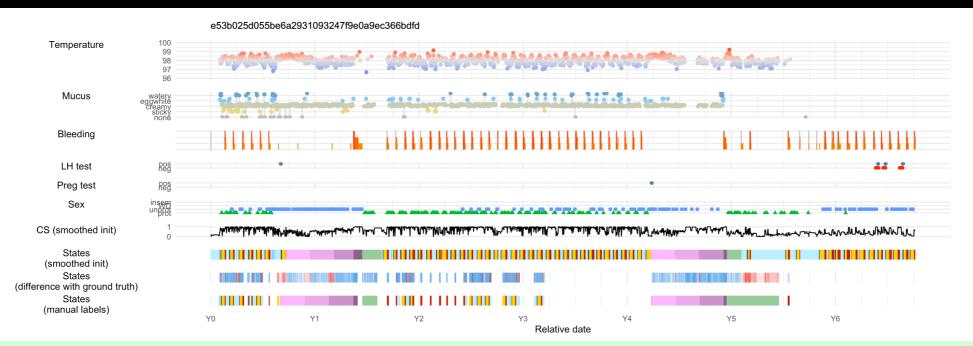
Upgraded 'hsmm' R package that

- can deal with high level of data missingness (as found in any digital health project)
- allows for any parametric or non-parametric distribution for the observed variables
 - which allow for discrete, categorical or continuous variables
- can quantify uncertainty by providing a confidence score for the decoded sequence,
 based on parametric bootstrap, independent of whether labelled data are available
- Available on my GitHub: @lasy

A statistical model that can accurately decode menstrual/fertility app data at different time-scale:



Conclusions

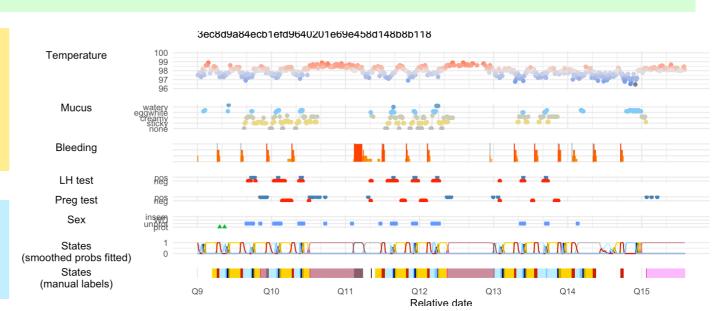


Upgraded 'hsmm' R package that

- can deal with high level of data missingness (as found in any digital health project)
- allows for any parametric or non-parametric distribution for the observed variables
 - which allow for discrete, categorical or continuous variables
- can quantify uncertainty by providing a confidence score for the decoded sequence,
 based on parametric bootstrap, independent of whether labelled data are available
- Available on my GitHub: @lasy

A statistical model that can accurately decode menstrual/fertility app data at different time-scale:

> About 200k users time-series labelled. Now we can interrogate these data.



Stanford University **Prof. Holmes**



Stanford University **Prof. Hillard**



Columbia University **Prof. Martinez**



Stanford University **Prof. Holmes**



Stanford University **Prof. Hillard**



Columbia University **Prof. Martinez**







sympto.org

Stanford University **Prof. Holmes**



Stanford University **Prof. Hillard**



Columbia University **Prof. Martinez**







sympto.org

Funding

Stanford University **Prof. Holmes**



Stanford University **Prof. Hillard**



Columbia University **Prof. Martinez**







sympto.org

Funding



Postdoc Mobility

FONDS NATIONAL SUISSE
SCHWEIZERISCHER NATIONALFONDS
FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

Stanford University

Clinical Data Science fellowship