Agenda today

- Discussion about what makes a good hypothesis
  - from groups of 3
  - formulate a precise hypothesis
  - submit it via menti.com (**6568 1361**)
- Developing a model of a physiological process

Developing simple Excel models of physiological processes

Dynamic Modelling for Human-centered Systems

Course outline

- Previous lecture: what is dynamic modelling?
- Current lecture: creating models of physiological processes
- Next lecture: creating models of social processes
- Later: modelling behaviour
- Even later: embedding models within intelligent systems…

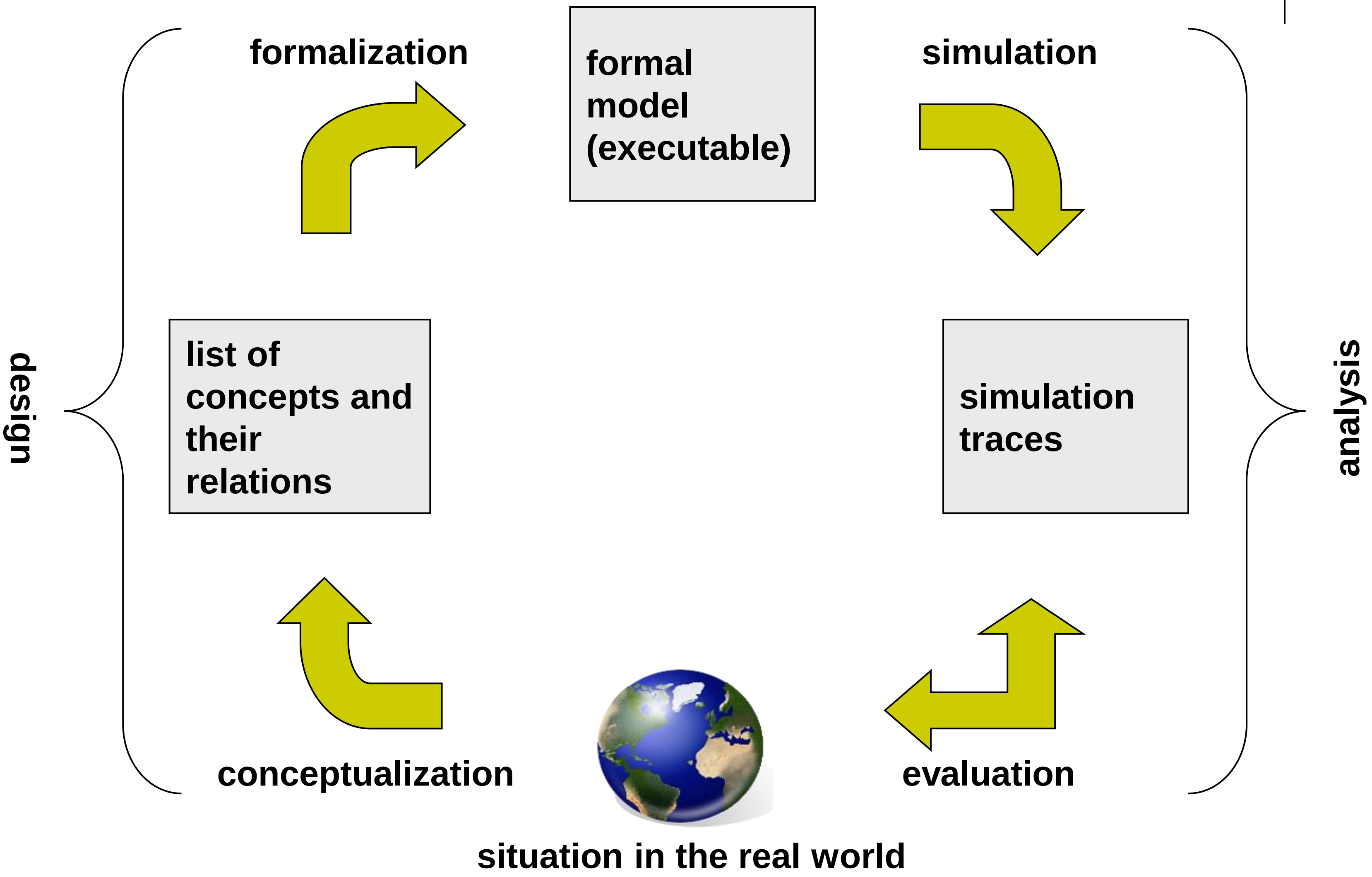
domain models

Which processes will we model?

- ~~Food intake of bacterium~~
- Responses of sea hare on stimuli

- At the same time:
  - rudimentary decision making process
  - neurally-inspired learning process
- *Building blocks for other models!*

Modelling and Simulation Cycle



Steps

1. **Conceptualisation**: identification of important concepts and relations
2. **Formalisation**: describe concepts and relations in an unambiguous way
3. **Simulation**: running experiments with models to generate simulations traces
4. **Evaluation**: verify whether the simulations are in line with expectations (properties)

Creating models in practice

- Biological knowledge is basis
- Similar approach for all models in syllabus:
  - study domain literature (syllabus section 1)
  - identify main aspects + relations (syllabus section 2)
    - also “characteristic patterns”
  - create formal representation (syllabus section 3)
  - perform simulations (syllabus section 4)
  - evaluate simulations (syllabus section 5)

Syllabus: Chapter 3

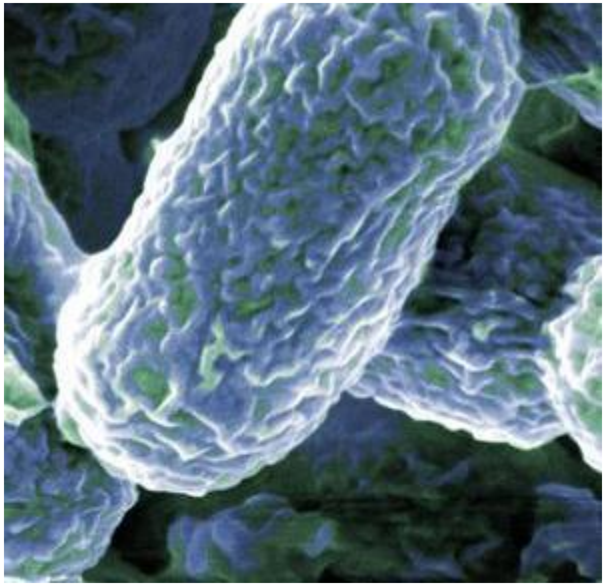
MODELLING FOOD INTAKE BY E-COLI

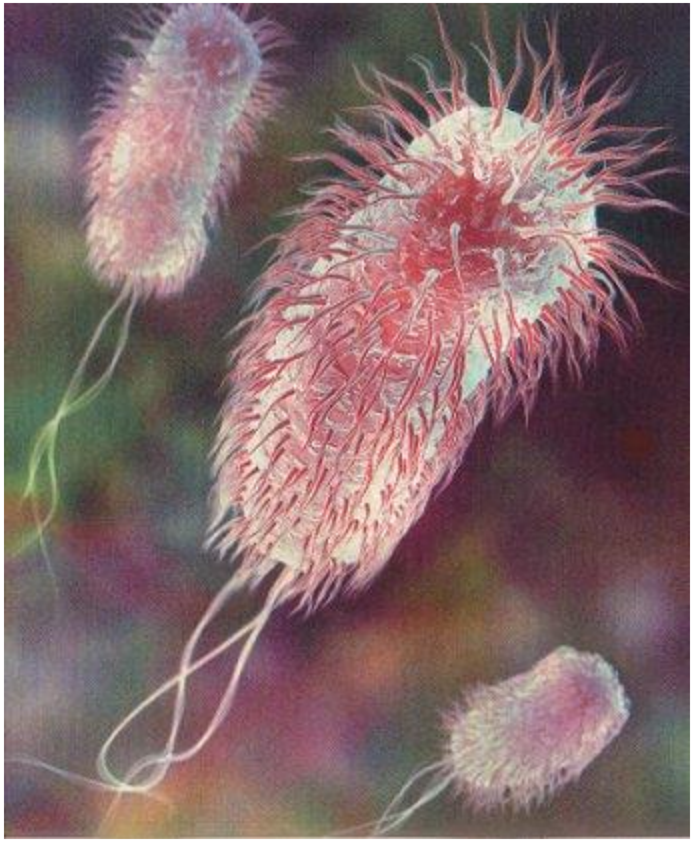
Modelling decision making

- How does *decision making* work?
- Complex process
  - much research about patterns
    - psychological experiments
    - decision models
  - underlying mechanism are difficult to study
    - *brain imaging* only shows activity of brain areas
  - bacterium is simple enough to understand chemical pathways

Bacterial food intake

- E-Coli: bacterium
  - located in intestines
  - consumes glucose or lactose





Behaviour bacter

Assignment

- Which pattern do you see in the behaviour of the bacterium?
- take 1 minute

	0	1	2	3	4	5	6
observation	glucose	glucose lactose	lactose	lactose	glucose lactose	glucose lactose	glucose lactose
action		import glucose	import glucose	import lactose	import lactose	import glucose	import glucose

Pattern

- Food intake behaviour:
  - At any point in time
    if it observes that - at previous time point -
    glucose is present,
    then it will import glucose

  - At any point in time,
    if it observes that - at previous time point –
    lactose is present,
    and that no glucose is present,
    then it will import lactose

Internal mechanism

- Bacterium can “observe” the environment (sensoring) and “decide” about
  - **lactose** intake, or
  - **glucose** intake
- Intake of lactose or glucose is controlled by two specific ***enzymes***
- “Lactose intake enzyme” is produced if:
  - chemical substance CRPcAMP is present, and
  - (low) concentration of lactose in cell

Internal mechanism (2)

- Substances in cell:
  - CRPcAMP is *only* present within cell if glucose is <0.1 mmol/l outside the cell
    - indicator of *absence* of glucose
  - a little bit of lactose is present in cell when there is lactose outside the cell (infiltrates)
- The bacterium will grow from both lactose intake as glucose intake

Characteristic patterns

- If a sufficient amount of any food (lactose or glucose) is externally present, then a substantial amount of food will be internally present
- If food is present, then the bacterium will grow
- If lactose is externally present, but not glucose, then lactose is imported,
- If glucose is externally present but not lactose, then glucose is imported,
- If both glucose and lactose are externally present, then glucose is imported but not lactose.

Assignment

- Which concepts do you think are relevant?
- Make a list of concepts
- *3 minutes*
- *groups of three; I will ask a few of you to come up with suggestions*

- Important question:
  - what do we consider as concepts?

Concepts

External state

Internal states reflecting the external state

Internal states for action initiation

Action performance

Internal state showing the effect of actions

Conceptualisation

External state

- glucose externally present
- lactose externally present

Internal states reflecting the external state

- CRPcAMP internally absent (glucose indicator)
- some lactose internally present (lactose indicator)

Internal states for action initiation

- enzyme for glucose import present
- enzyme for lactose import present

Action performance

- glucose import takes place
- lactose import takes place

Internal state showing the effect of actions

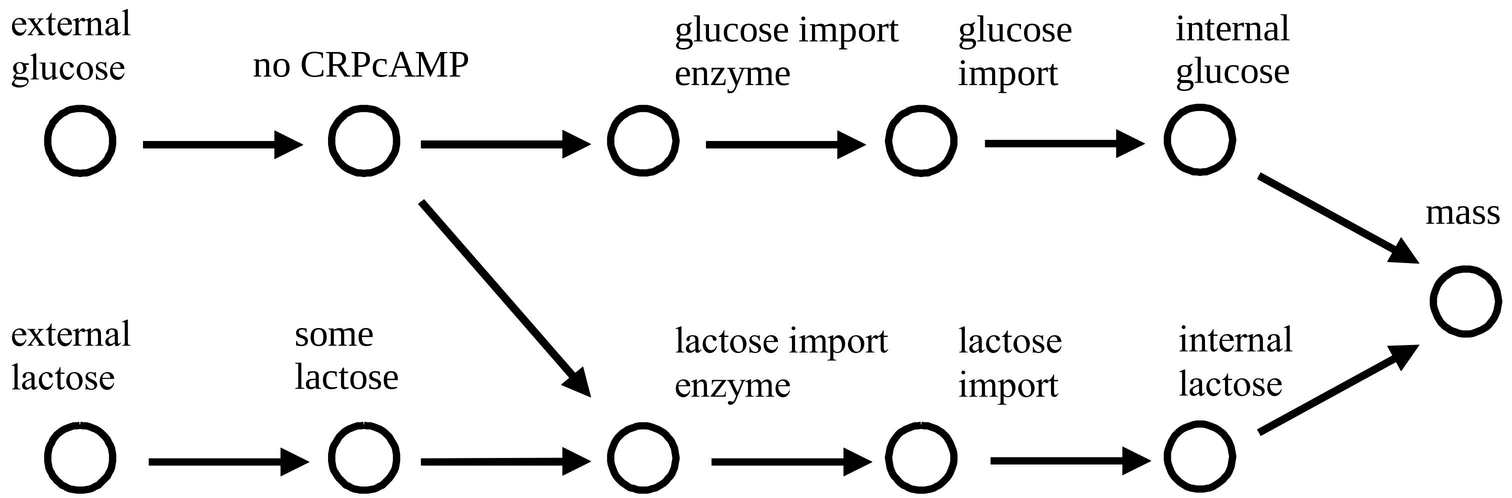
- substantial glucose internally present
- substantial lactose internally present
- mass

Assignment

- Which direct relations can be identified between the concepts?
- Draw a diagram with circles for concepts and arrows between concepts if a concept affects another concept.
- *10 minutes*
- *create powerpoint / google sheet to share*

Conceptualisation (2)

- "Affects" relations between concepts



Formalisation of concepts

- Variables for every concept
  - glucose externally present: *EXTgluc* [0/1]
  - lactose externally present: *EXTlac* [0/1]
  - glucose indicator (no CRPcAMP): *glucIND* [0/1]
  - lactose indicator: *lacIND* [0/1]
  - glucose import enzyme: *glucimpENZ* [0/1]
  - lactose import enzyme: *lacimpENZ* [0/1]
  - glucose internally present: *INTgluc* [0/1]
  - lactose internally present: *INTlac* [0/1]
  - mass: *M* [real]

Formalisation of relations

- Example relations:
  - From external glucose to glucose indicator
    - $glucIND\ (t+\Delta t) \ = \ EXTgluc(t)$
  - From lactose and glucose indicator to enzyme for lactose import
    - $lacimpENZ(t+\Delta t) \ = \ lacIND(t)*(1 - glucIND(t))$
  - Effect on mass
    - $M(t+\Delta t) \ = \ M(t) + \gamma\,(\ INTgluc(t) + INTlac(t))*M(t)$

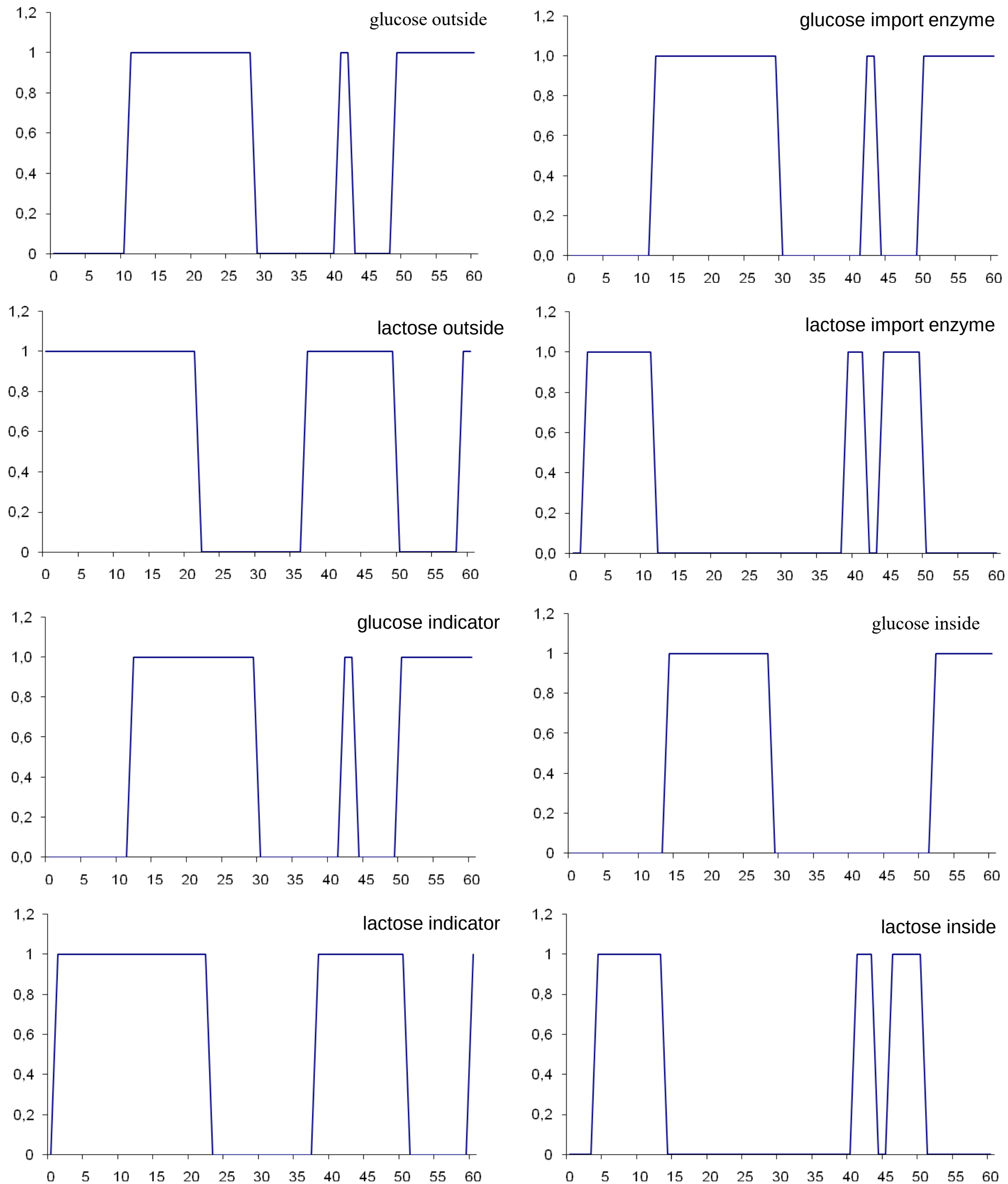
- *Almost logical representation*

Formalisation (2)

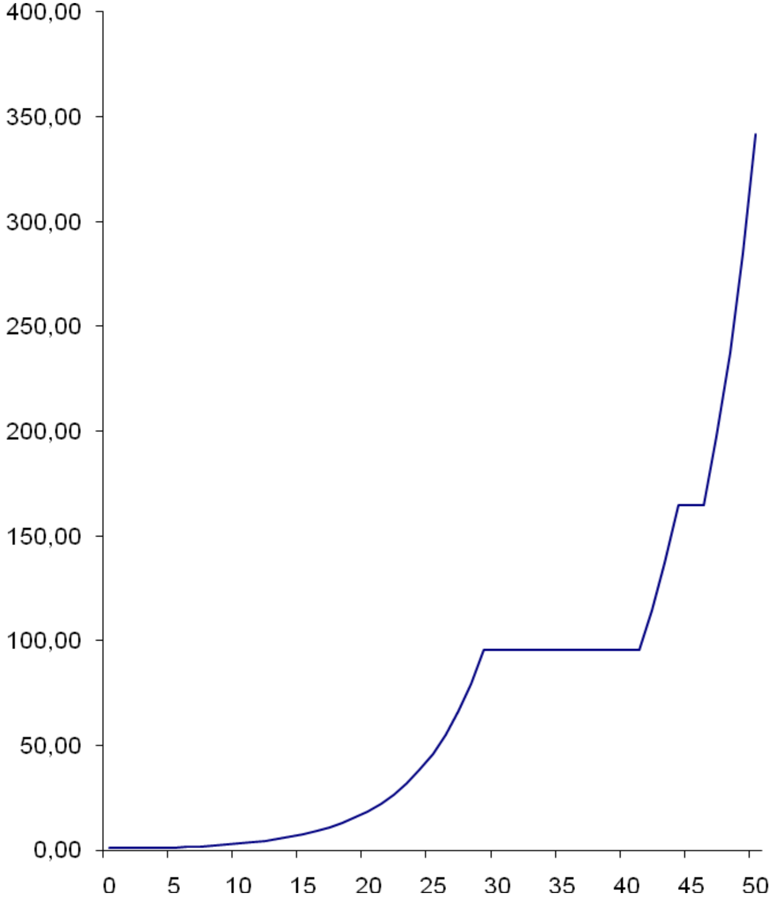
- Dependencies

t	int gluc	int lact	mass	add mass	γ
0	1	0	1	0.20	0.2
1	0	1	1.2	0.24	0.2
2	0	1	1.44	0.29	0.2
3	0	1	1.73	0.35	0.2
4	0	1	2.08	0.42	0.2
5	0	1	2.50	0.50	0.2

Simulation experiments



Simulation bacteria growth



Evaluation

- Characteristic patterns:
  - If a sufficient amount of any food (lactose or glucose) is externally present, then a substantial amount of food will be internally present
  - If food is present, then the bacterium will grow
  - If lactose is externally present, but not glucose, then lactose is imported,
  - If glucose is externally present but not lactose, then glucose is imported,
  - If both glucose and lactose are externally present, then glucose is imported but not lactose.

Summary

- Food intake by bacteria can be modelled numerically
  - extensions with role of DNA and mRNA are possible

    = see reader

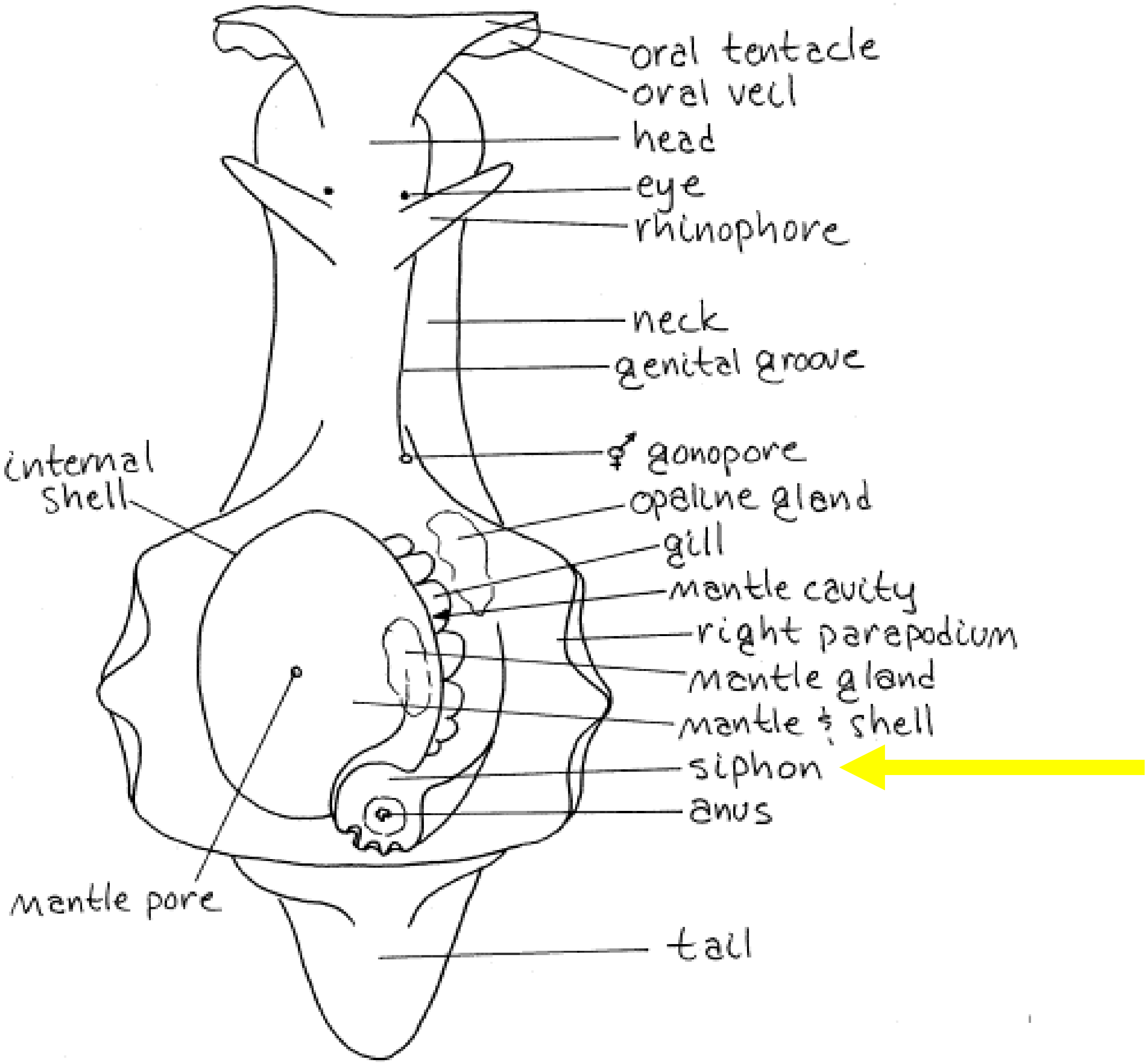
Syllabus: Chapter 4

NEURAL MECHANISM FOR LEARNING

Aplysia

- Aplysia is a sea hare that is often used to do experiments.
  - for example, it performs classical conditioning: learning to move upon a siphon touch.

Aplysia



- The siphon is a spot on the back of the animal.

Behaviour Before Learning Phase

- Initially the following behaviour is shown:
  - a tail shock leads to a response (moving: contraction)
  - a light touch on its siphon is insufficient to trigger such a response

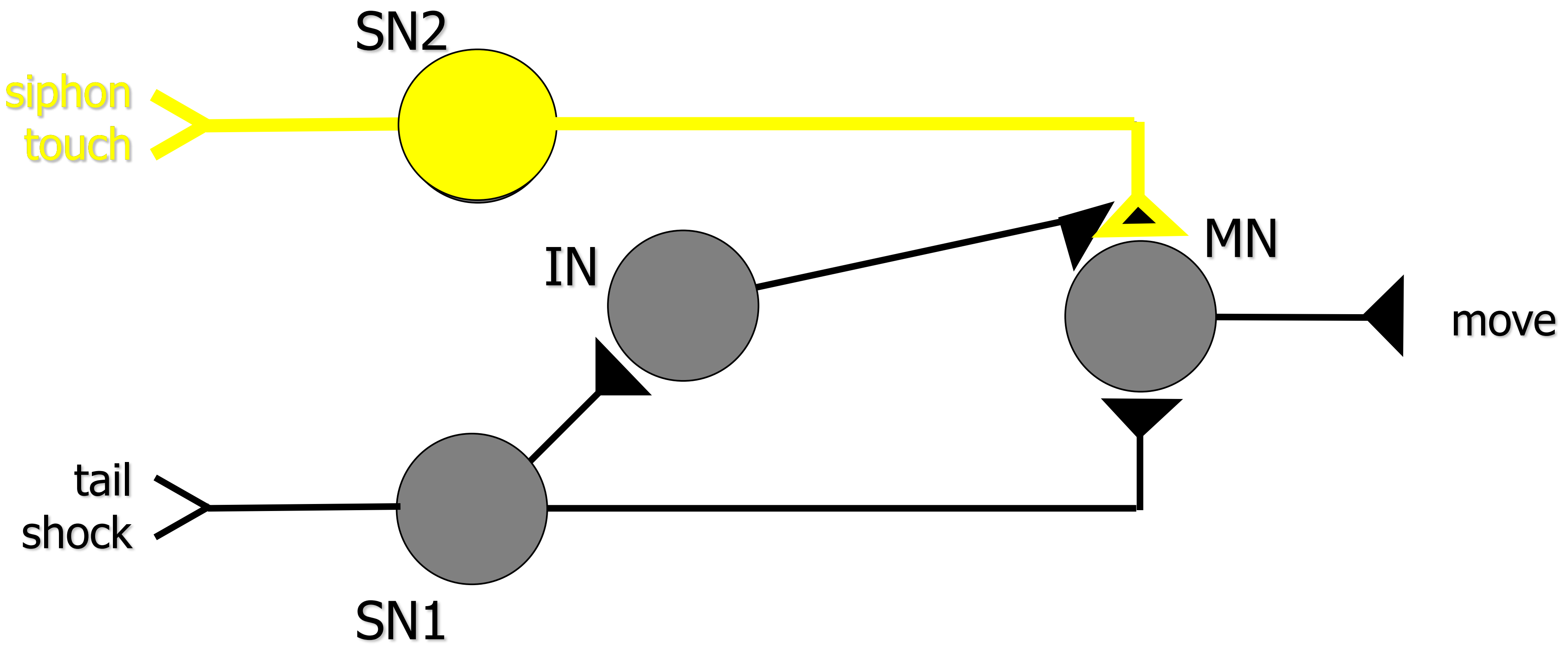
Behaviour After a Learning Phase

- It turns out that after a number of trials the behaviour has changed (adapted behaviour):
  - the animal also responds (moving) on the siphon touch

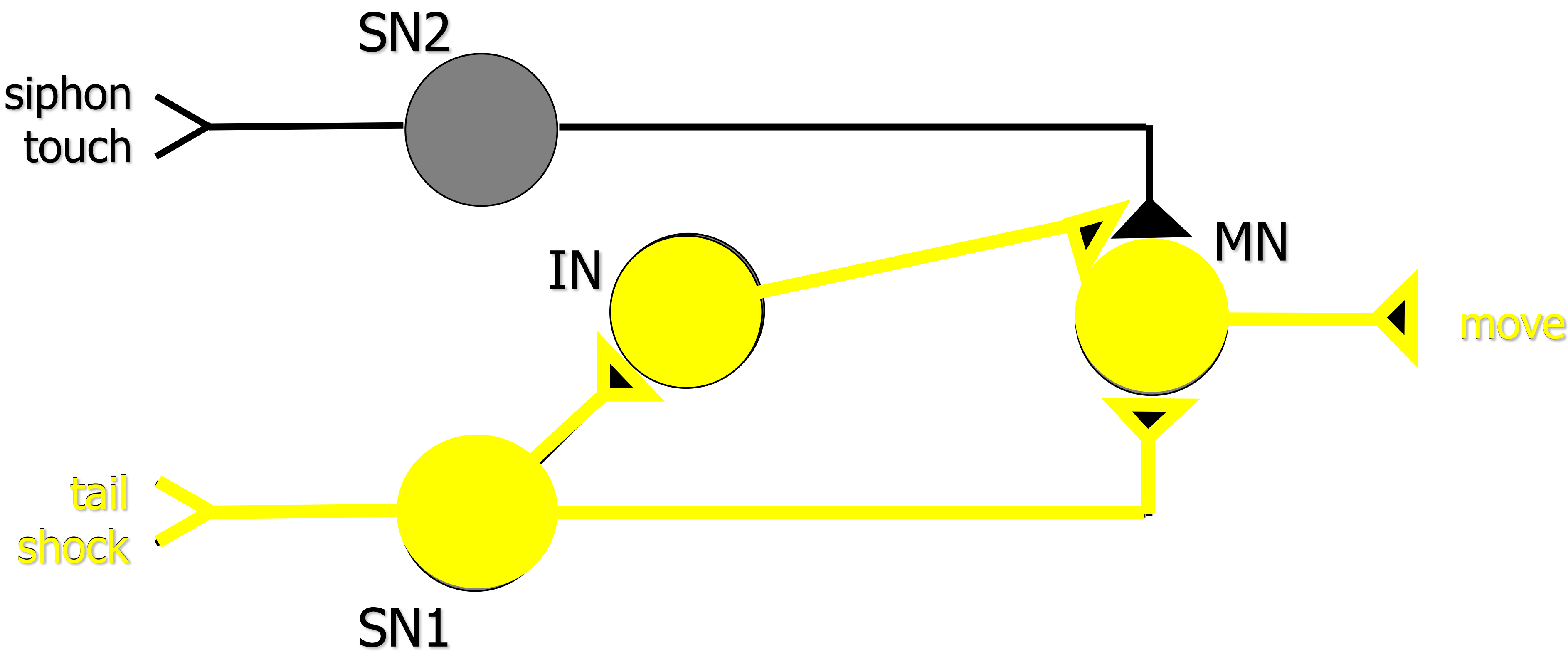
Training Aplysia

- Protocol for training an Aplysia:
  - a number of trials
  - in each trial:
    - the subject is touched lightly on its siphon
    - then, shocked on its tail
    - as a consequence it responds

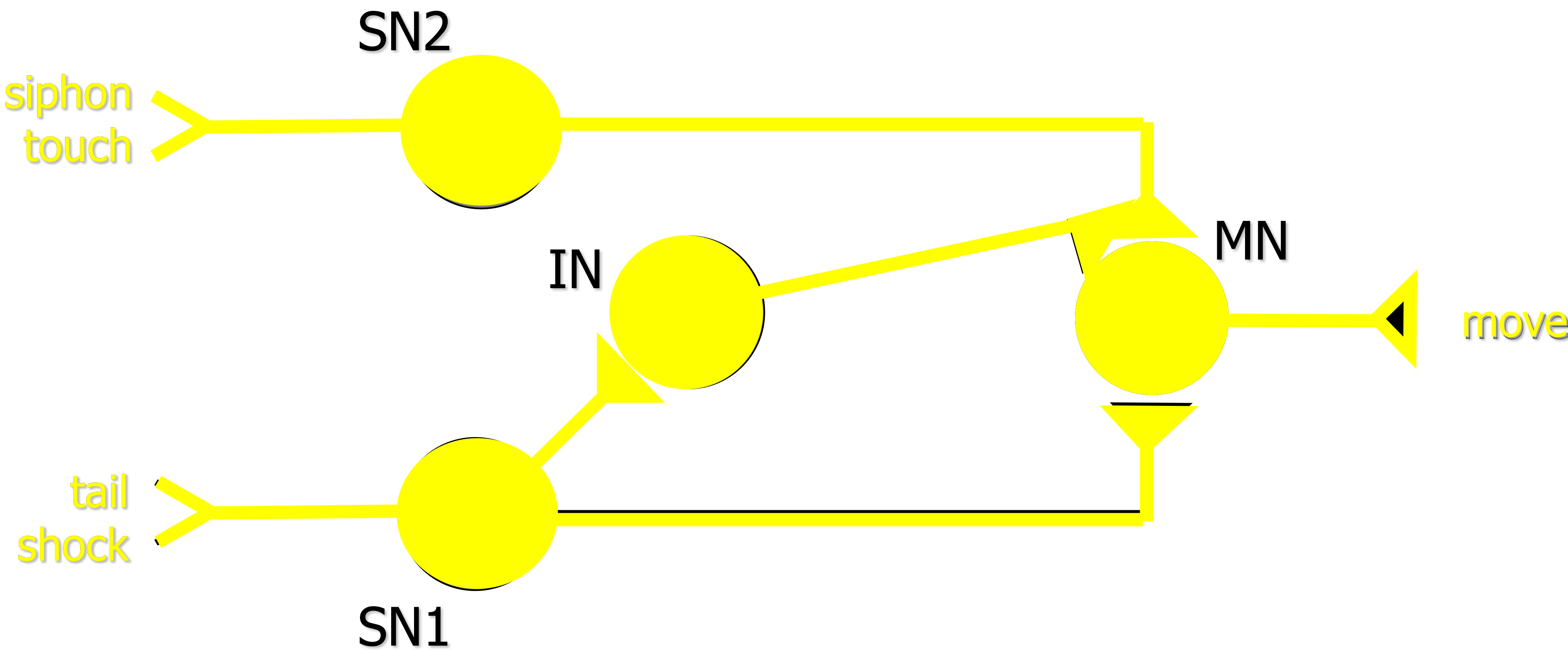
Neural Mechanism: Siphon Touch



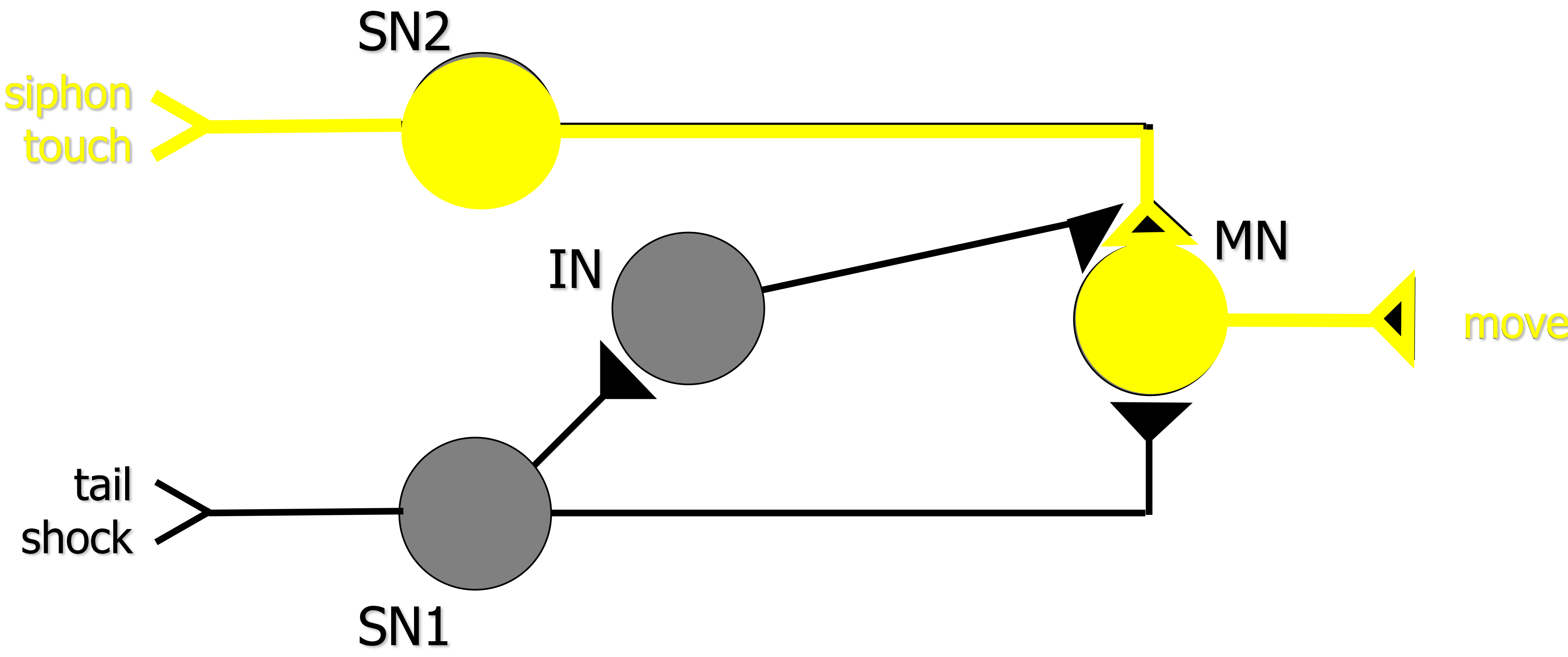
Neural Mechanism: Tail Shock



Neural Mechanism: Learning



Neural Mechanism:
Learned Siphon Touch Response

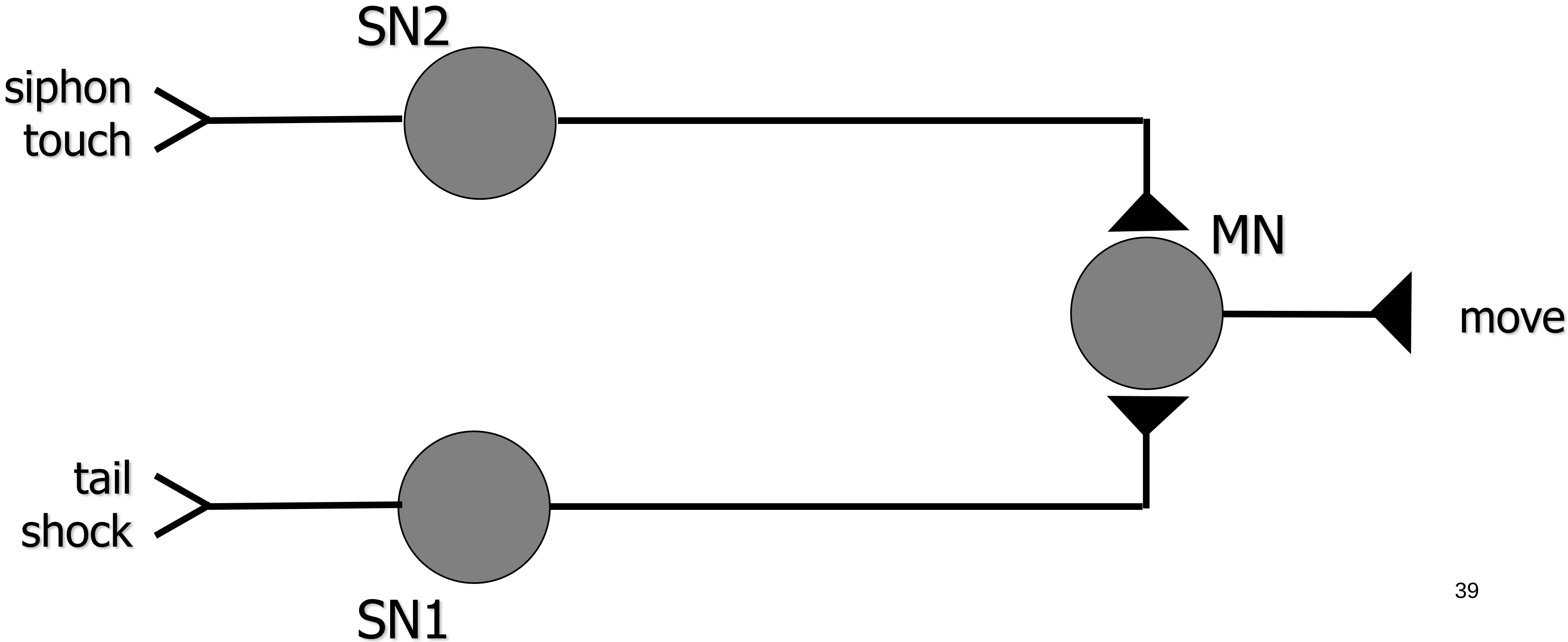


Simplified Learning Principle

- If both SN2 and IN are activated simultaneously, this changes the synapse between SN2 and MN:
- It makes that in this synapse more neurotransmitter is produced if SN2 is activated.
- After a number of times this leads to the new situation that also activation of SN2 leads to activation of MN.

Modeling Aplysia learning

- Conceptualization
- Simplification: no intermediate neuron IN



Assignment

- Which concepts do you think are relevant?
- Make a list of concepts
- *3 minutes*
- *groups of three; I will ask a few of you to come up with suggestions*

- Important question:
  - what do we consider as concepts?

Concepts

- tail shock
- siphon touch
- contraction
- sensory neuron SN1 is activated
- sensory neuron SN2 is activated
- motoneuron MN is activated

Relations

Sensory processes

- A tail shock affects activation of SN1
- A siphon touch affects activation of SN2

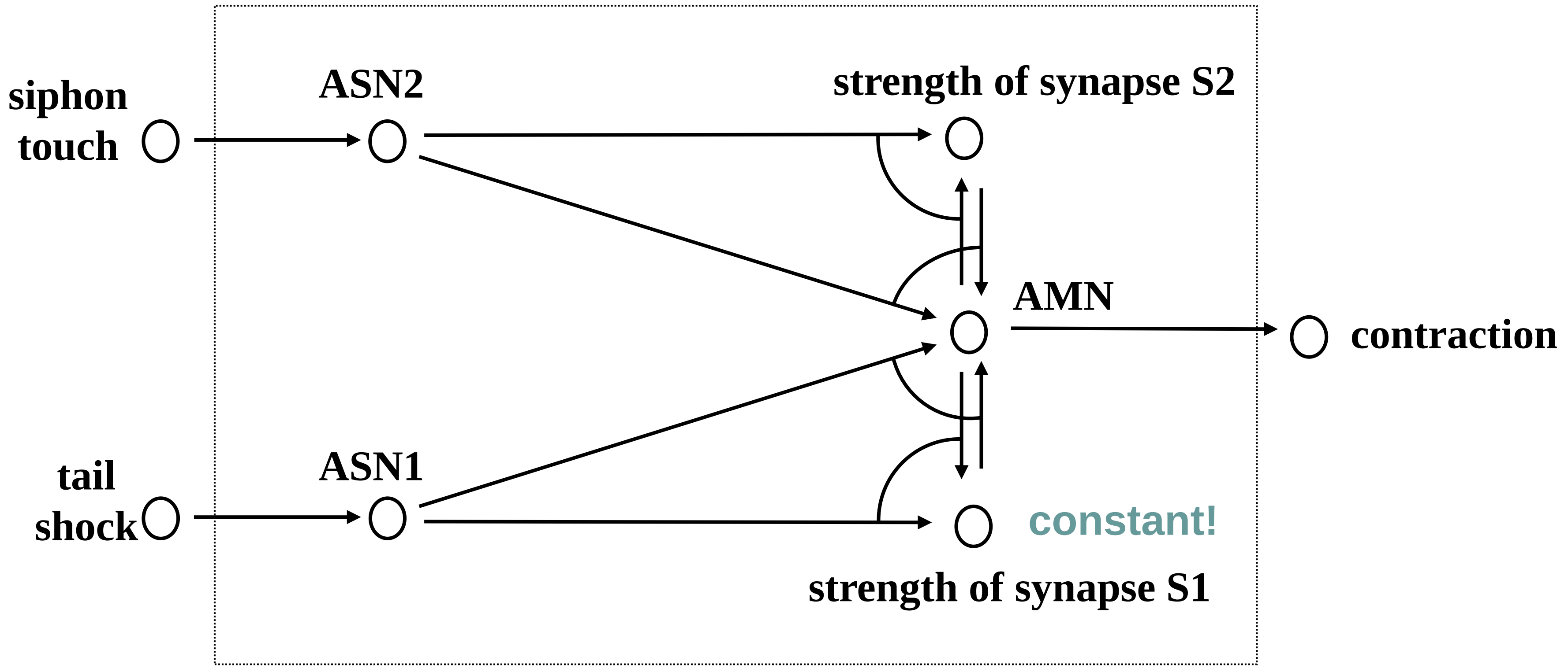
Action generation

- Activation of SN1 affects activation of MN
- Activation of SN2 together with a certain strength of synapse S2 affects activation of MN
- Activation of MN affects contraction

Adaptation

- Simultaneous activation of MN and SN2 affects the strength of synapse S2 between SN2 and MN by increasing it

Relations between concepts



Expected patterns:

- Initially a contraction occurs after a shock, but no reaction upon a siphon touch
- After a training period of a number of trials (each of a siphon touch followed by a tail shock), contraction will take place after any siphon touch
- During a training period the strength of the synapse increases and eventually reaches a maximal strength

Concepts (2)

- tail shock (*TailShock*)
- siphon touch (*SiphonTouch*)
- contraction (*Contraction*)
- sensory neuron SN1 is activated (*ASN1*)
- sensory neuron SN2 is activated (*ASN2*)
- motoneuron MN is activated (*AMN*)
- the synapse S1 between SN1 and MN has a certain strength (*S1*)
- the synapse S2 between SN2 and MN has a certain strength (*S2*)

Formalization

- Concepts:
  - events and neuron activation: [0/1]
  - synapse strength: integer
- Relations
  - From tail shock to activation of SN1
    - $ASN1(t+\Delta t) = max(TailShock(t), TailShock(t-\Delta t), TailShock(t-2\Delta t))$
  - From siphon touch to activation of SN2
    - $ASN2(t+\Delta t) = max(SiphonTouch(t), SiphonTouch(t-\Delta t), SiphonTouch(t-2\Delta t))$

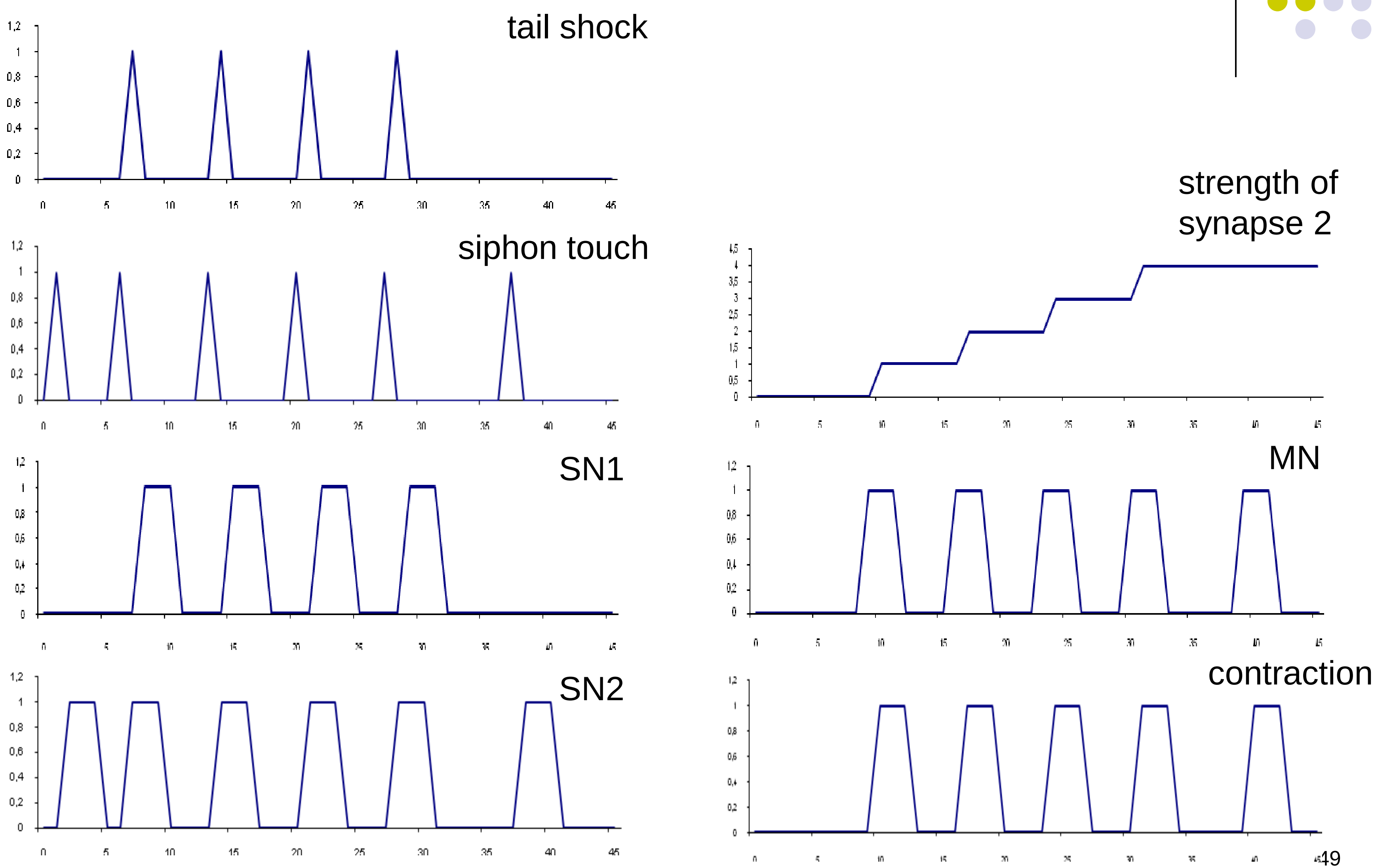
Formalization (2)

- From activation of MN to contraction
  - $Contraction(t+\Delta t) = AMN(t)$
- From activation of SN1 or SN2 to activation of MN
  - $$AMN(t+\Delta t) = \begin{cases} 1 & \text{if } ASN1(t) = 1 \text{ or: } \\ & S2(t) = 4 \text{ and } ASN2(t) = 1 \\ 0 & \text{else} \end{cases}$$
- Adjustment of the synapse strength based on simultaneous activation of MN and SN2
  - $$S2(t+\Delta t) = \begin{cases} S2(t) + 1 & \text{if } S2(t) < 4 \text{ and} \\ & AMN(t) = ASN2(t) = 1 \\ S2(t) & \text{else} \end{cases}$$

Temporal relations in Excel

t	tail shock	siphon touch	ASN1	ASN2	AMN	synapse S2	contrac-tion
0	0	0	0	0	0	0	0
1	1	0	0	0	0	0	0
2	0	1	1	0	0	0	0
3	0	0	1	1	0	0	0
4	0	0	1	1	1	0	0
5	0	0	0	1	1	1	1

Simulations



Discussion

- Assumptions and choices in the model
  - The adjustments of the synapse strength are linear: every trial the same increase, until a maximum is reached.
  - There is no decay of synapse strength.
  - Activations of neurons last three time steps.
  - In a training period the stimuli (siphon touch and tail shock) are presented at two successive time steps.

Discussion (2)

- Variations:
  - Faster or slower learning.
  - Activation of the motoneuron MN by sensory neuron SN2 can take place in case the strength of the synapse connecting them is above a certain threshold, not at a maximum value.
  - The adjustments of the synapse strength can be taken not linear but bounded by a maximum.
  - Decay of synapse strength can be incorporated.
  - The activation periods of neurons may be taken to last longer or shorter than three time steps.
  - In a training period the time difference between the two stimuli (tail shock and siphon touch) can be varied.