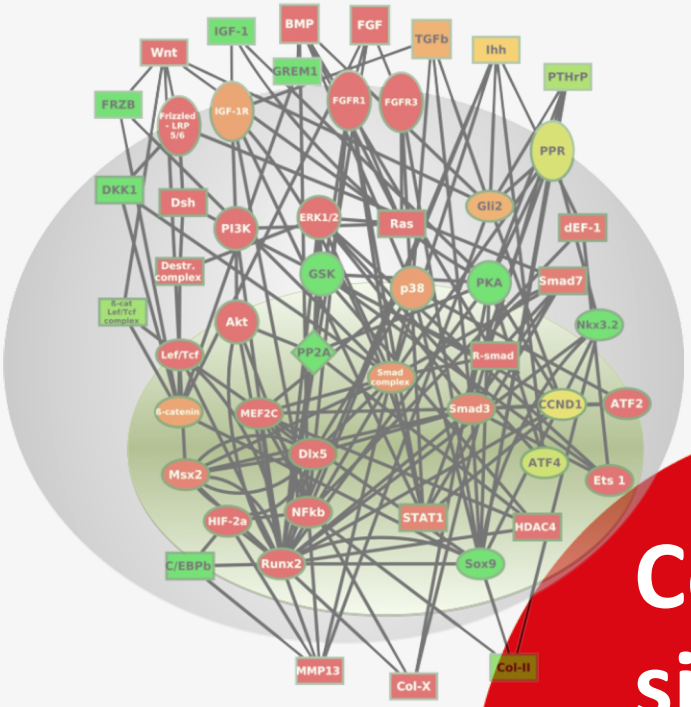
Open Universiteit




# Computational models in signal transduction research

*Convinces biologists that formal verification is actually a thing, hilarity ensues.*

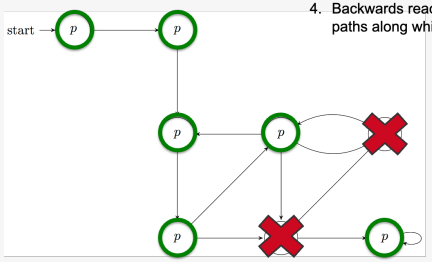
*Stefano Schivo*
*Joint works with many people*

# Formal Methods and Timed Automata

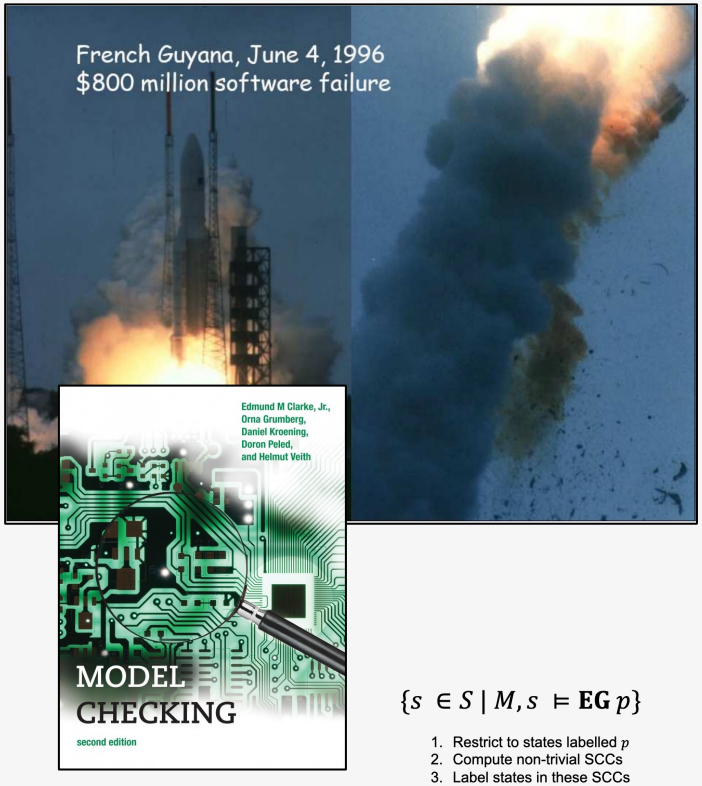
# Formal Methods and Timed Automata


$$\{s \in S \mid M, s \models \mathbf{EG}\, p\}$$

1. Restrict to states labelled $p$
2. Compute non-trivial SCCs
3. Label states in these SCCs
4. Backwards reachability to label paths along which $p$ holds



# Formal Methods and Timed Automata

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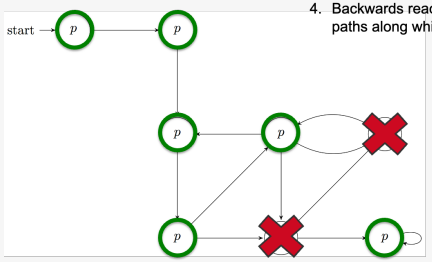
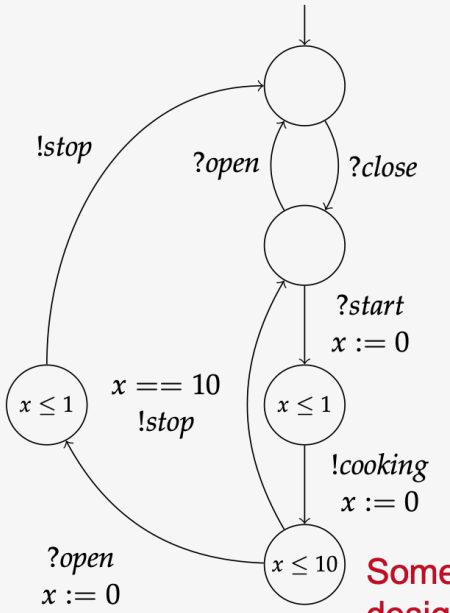



## Timed Automata: textbook definition

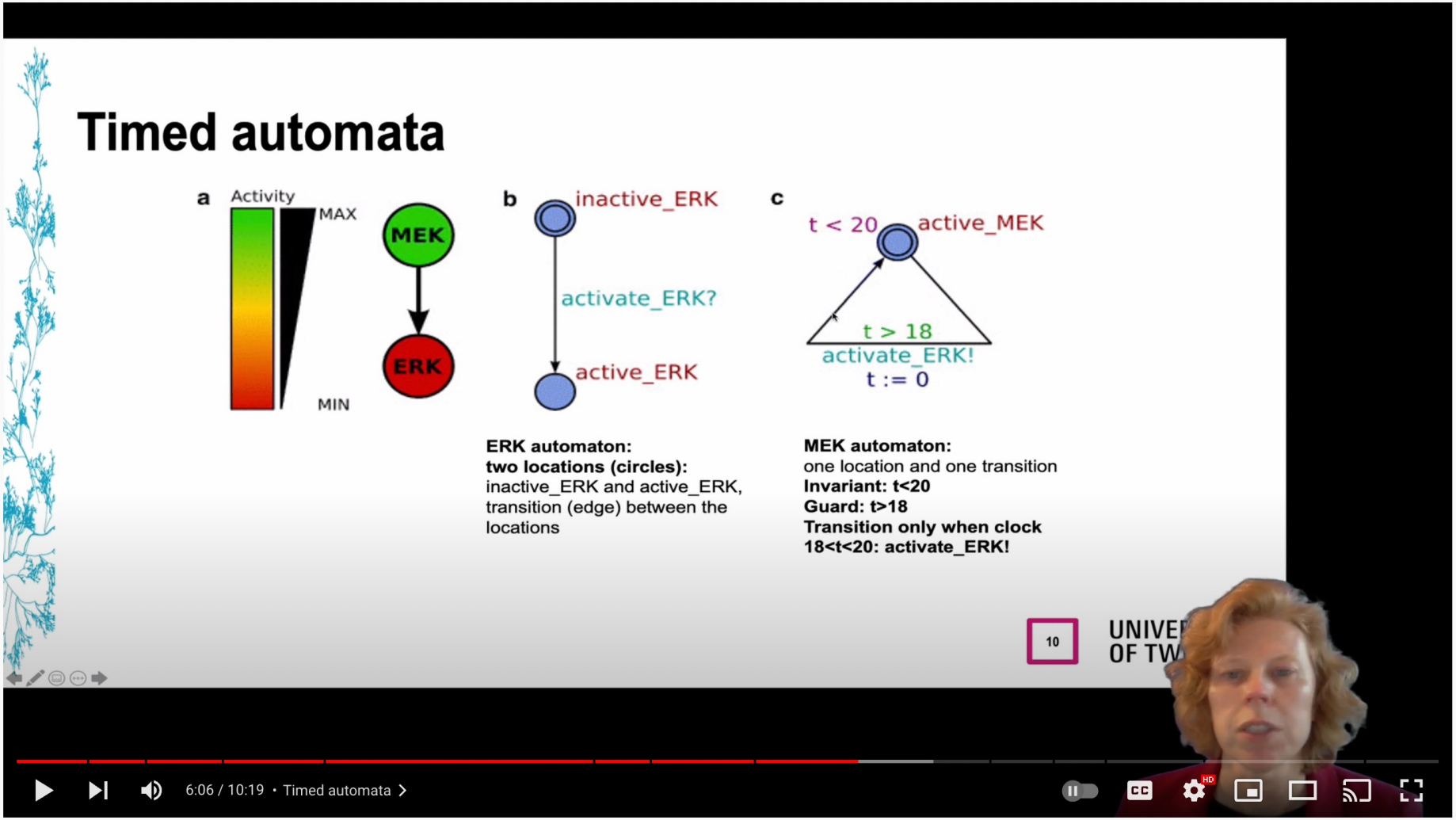
Real values (not just integers)!



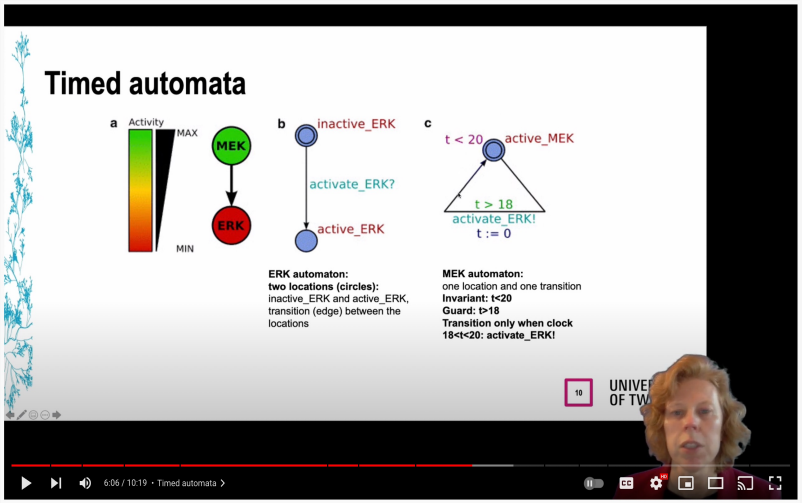

- Set of actions $\Sigma$
- Set of locations $S$
- Set of initial locations $S_0$
- Finite set of clocks $X$
- Function $I$ giving invariant $I(l)$ for each location
- Finite set of transitions $T$
  - Source location
  - Action (*synchronisation*)
  - Guard
  - Resets
  - Target location

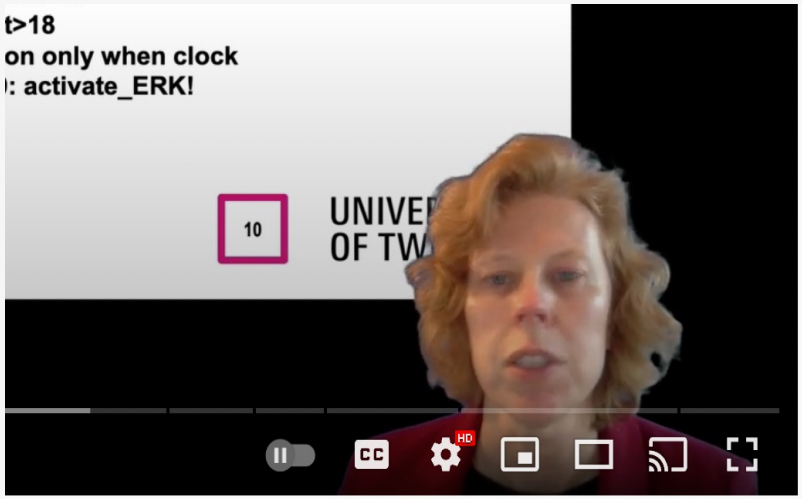
Sometimes actions designated input (?)/output (!)

# Explaining Timed Automata…



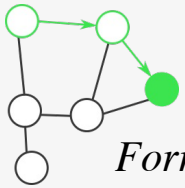
# *record scratch*  *freeze frame*



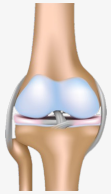




*Yup, that's a biologist. Explaining Timed Automata to biologists. You're probably wondering how she ended up in this situation.*

# How it all began

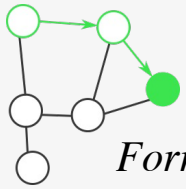



*Formal Methods and Tools*

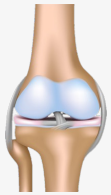


*Developmental BioEngineering*

# How it all began

*Human-Machine Interaction*



*Formal Methods and Tools*

*Developmental BioEngineering*

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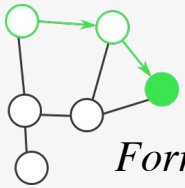

*Formal Methods and Tools*

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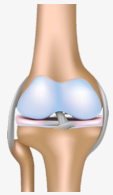
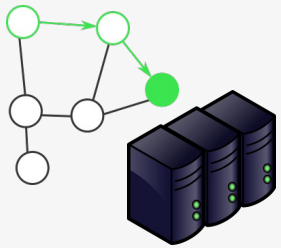


*Developmental BioEngineering*

# First contacts



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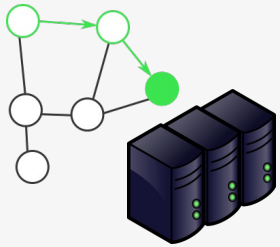

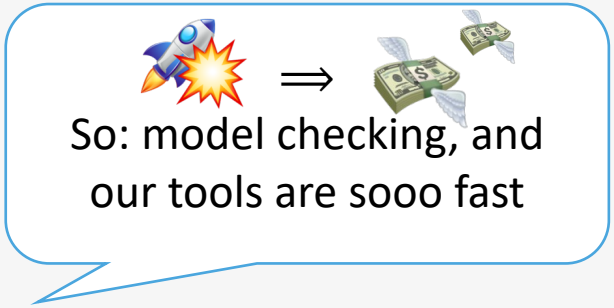


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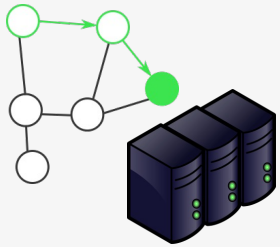
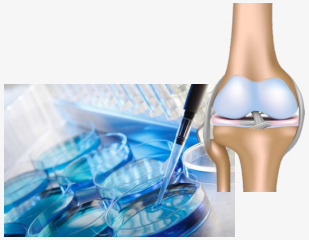
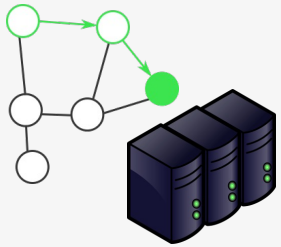


So: model checking, and our tools are sooo fast

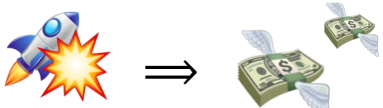


Why should this interest me?

# First contacts



*Has a hammer,*
*is looking for a nail*

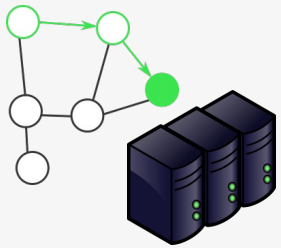


So: model checking, and our tools are sooo fast

*Wants to paint the wall yellow*

Why should this interest me?

# First contacts



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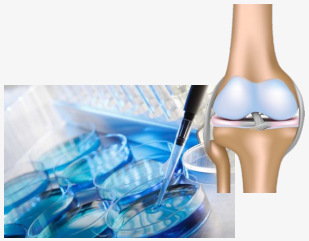
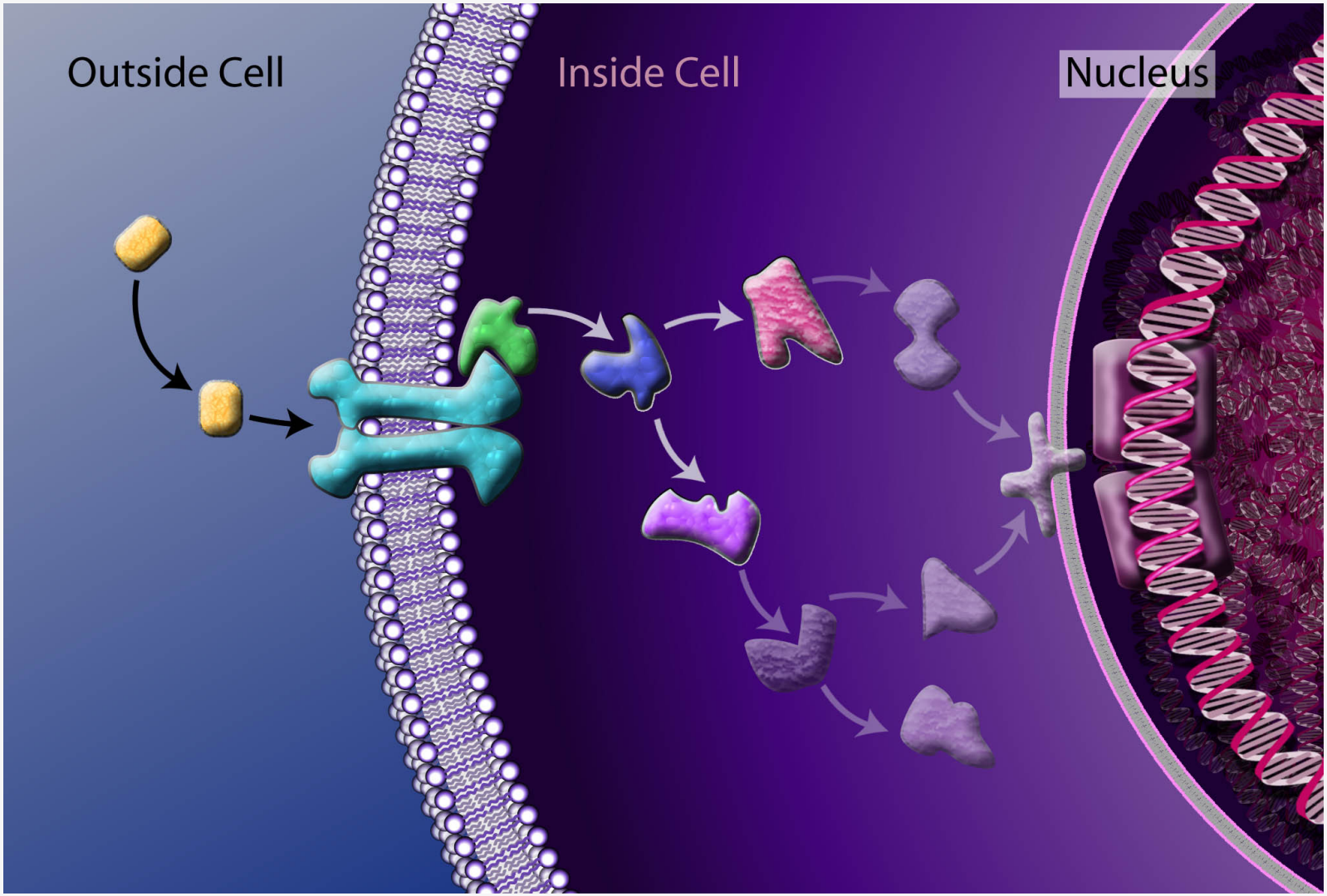


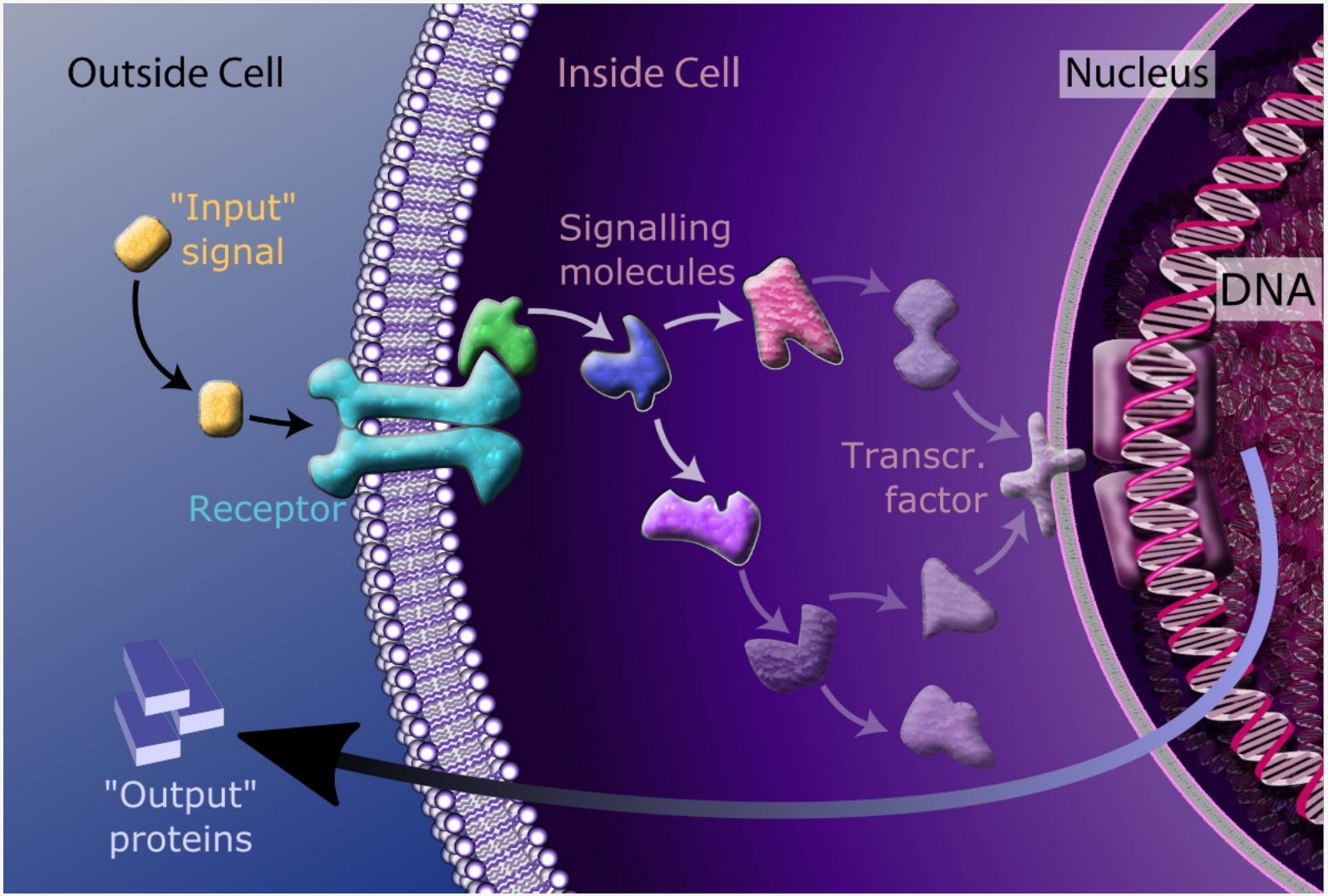
*Wants to paint*
*the wall yellow*

*Lesson #1: listen*

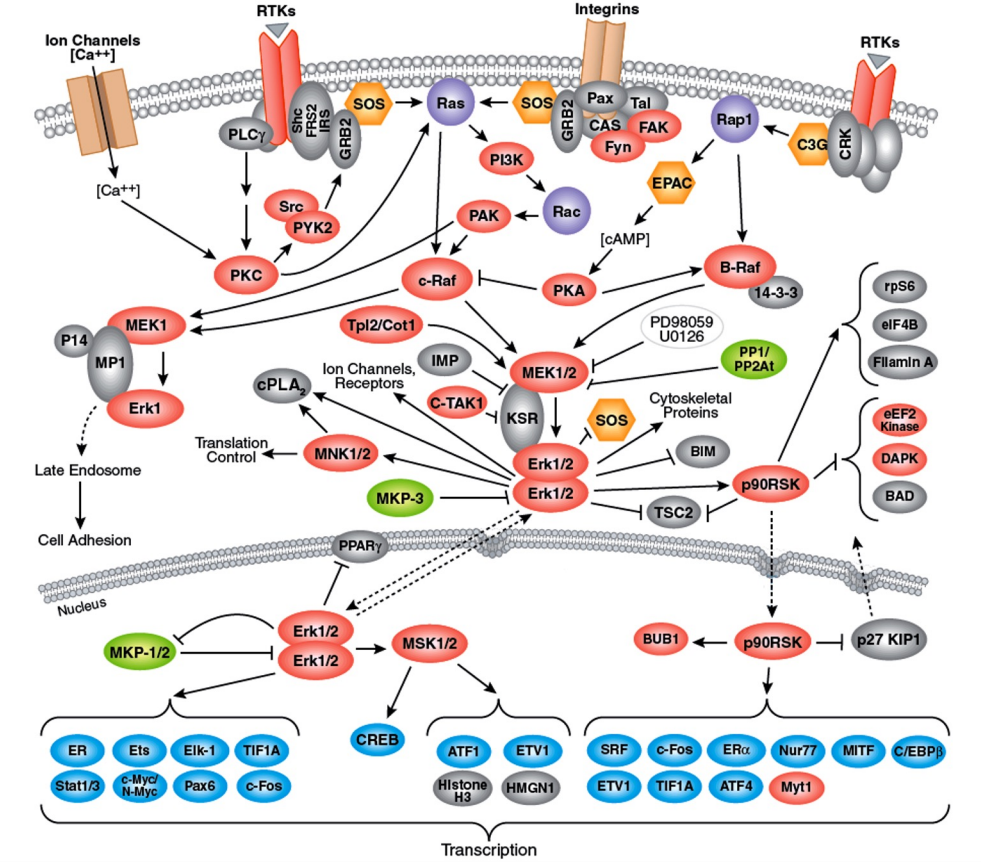
# Signalling pathways: a primer



# Signalling pathways: a primer



# Complex networks of interactions



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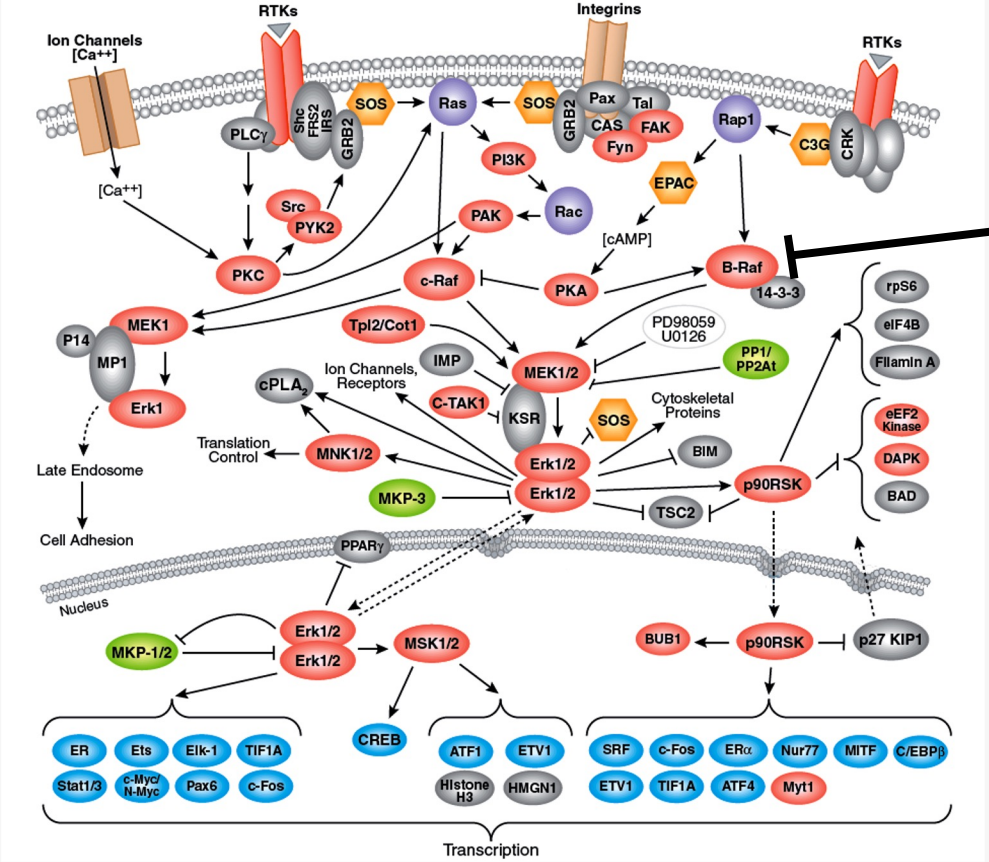
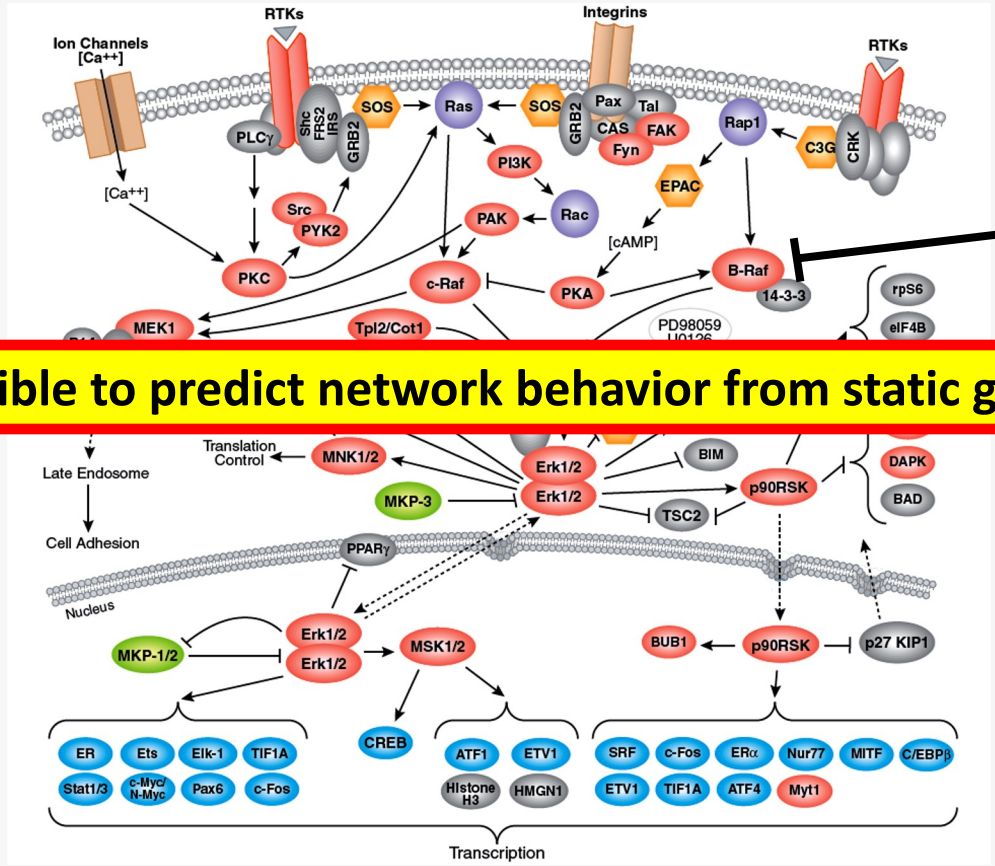


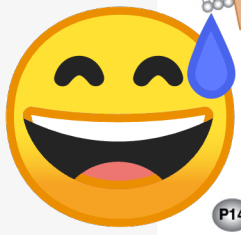
# Complex networks of interactions

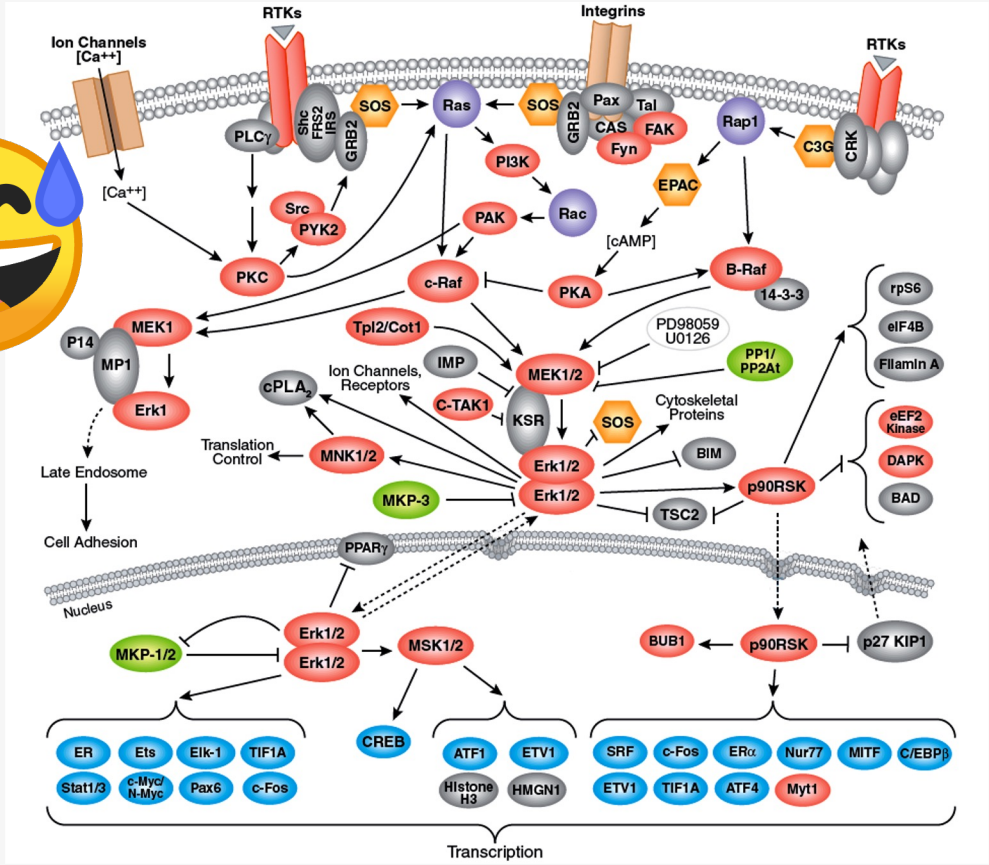



Drug

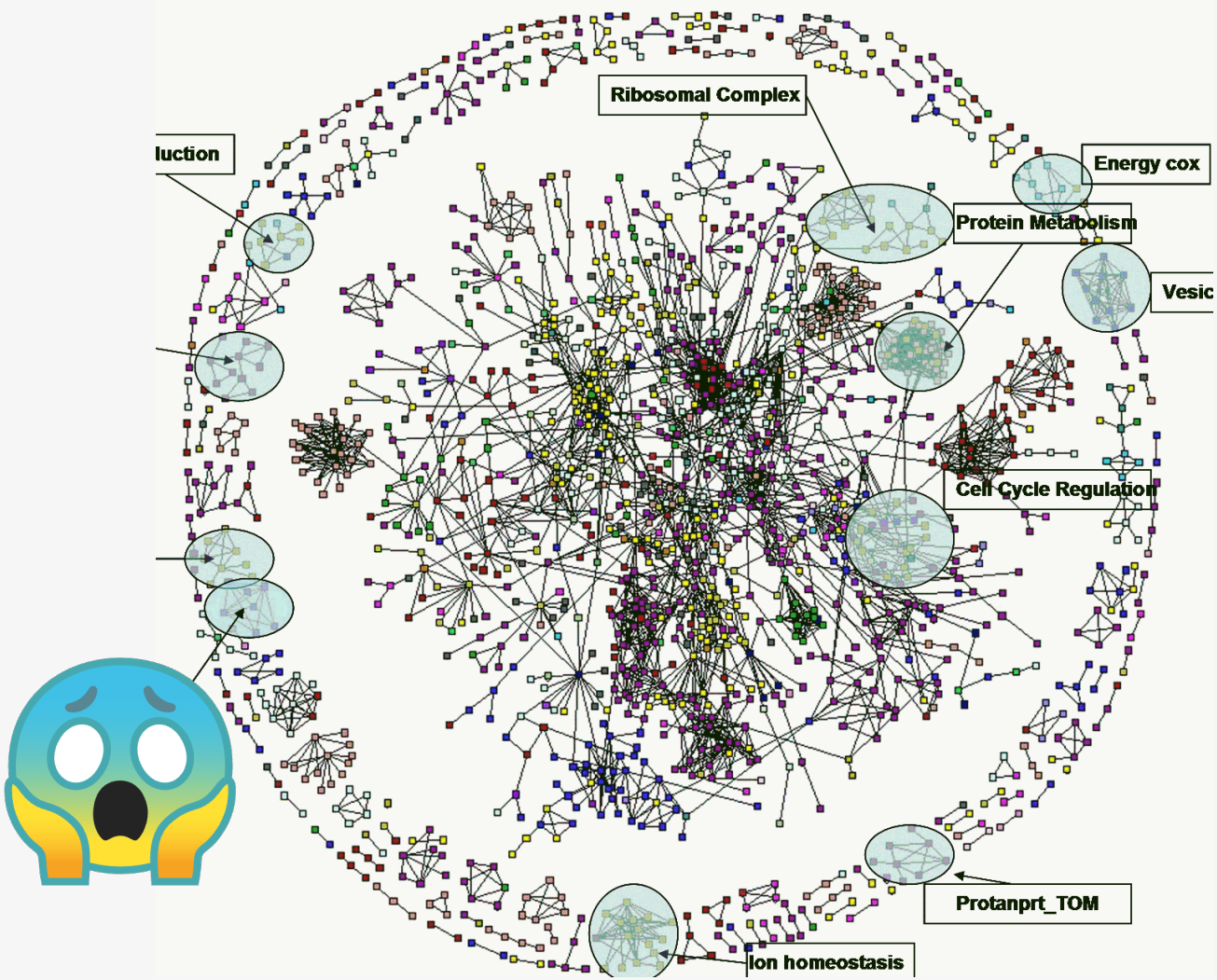
**Impossible to predict network behavior from static graphs!**

# The more we know…





# … The less we understand



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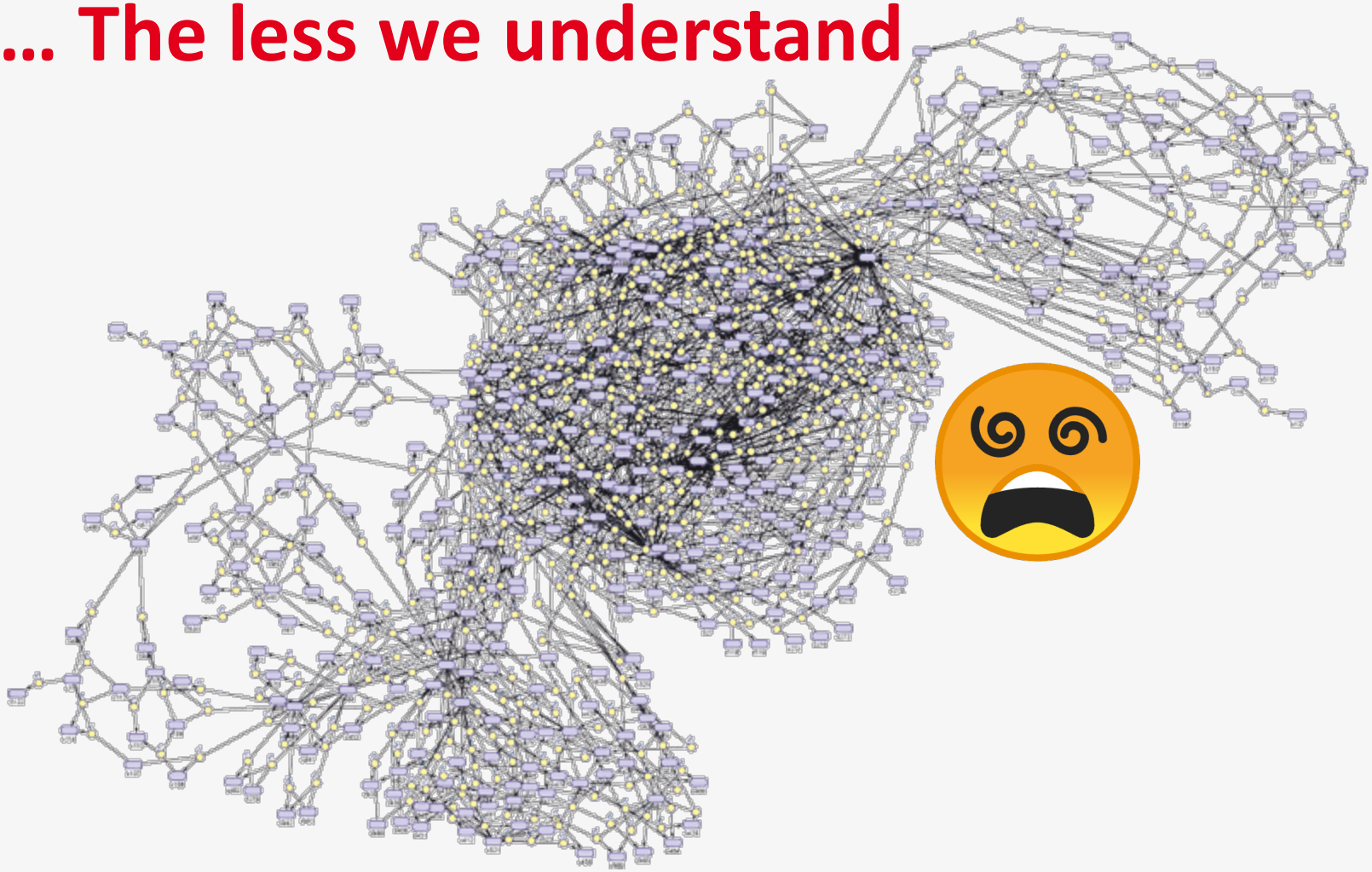

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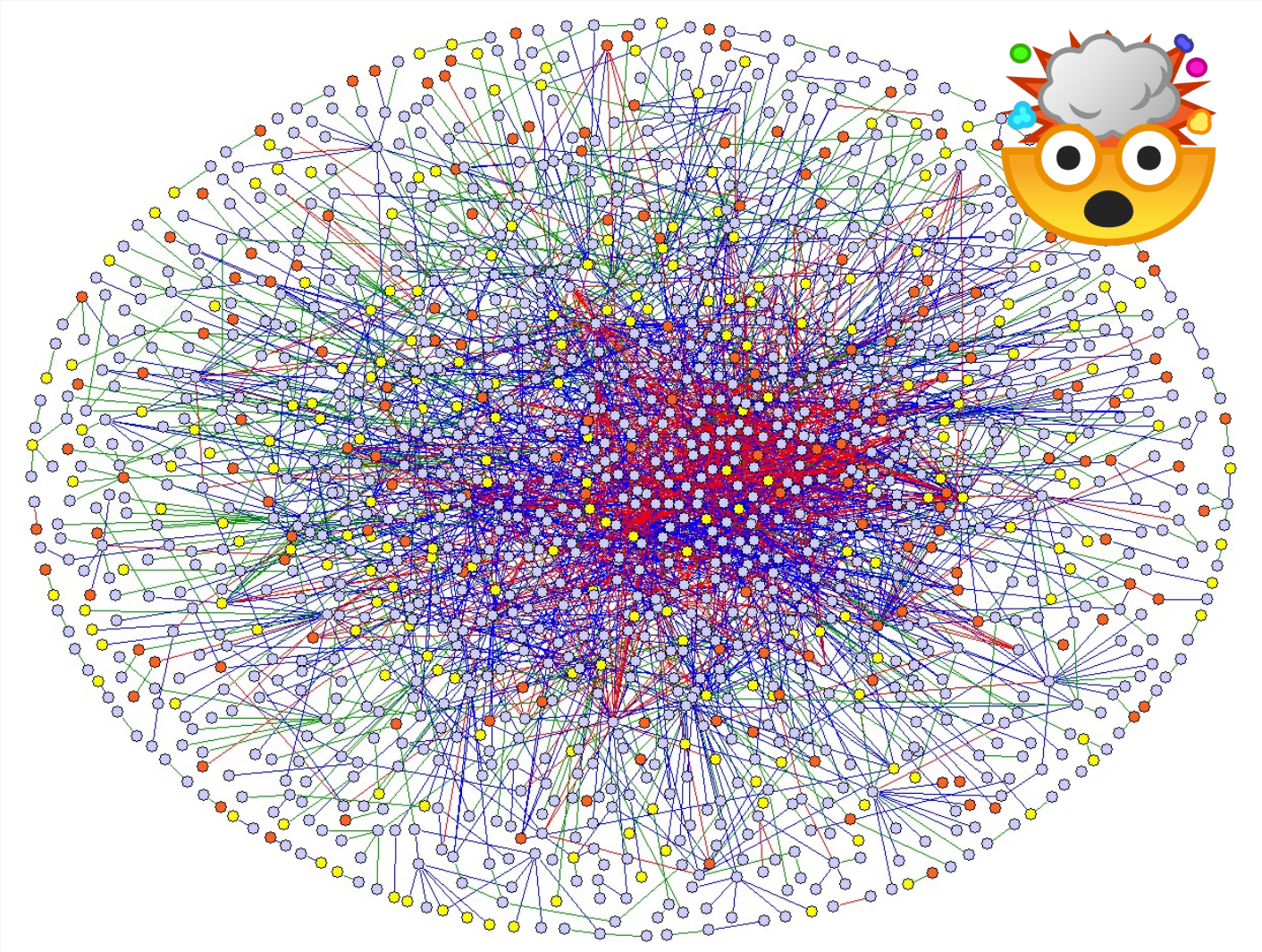
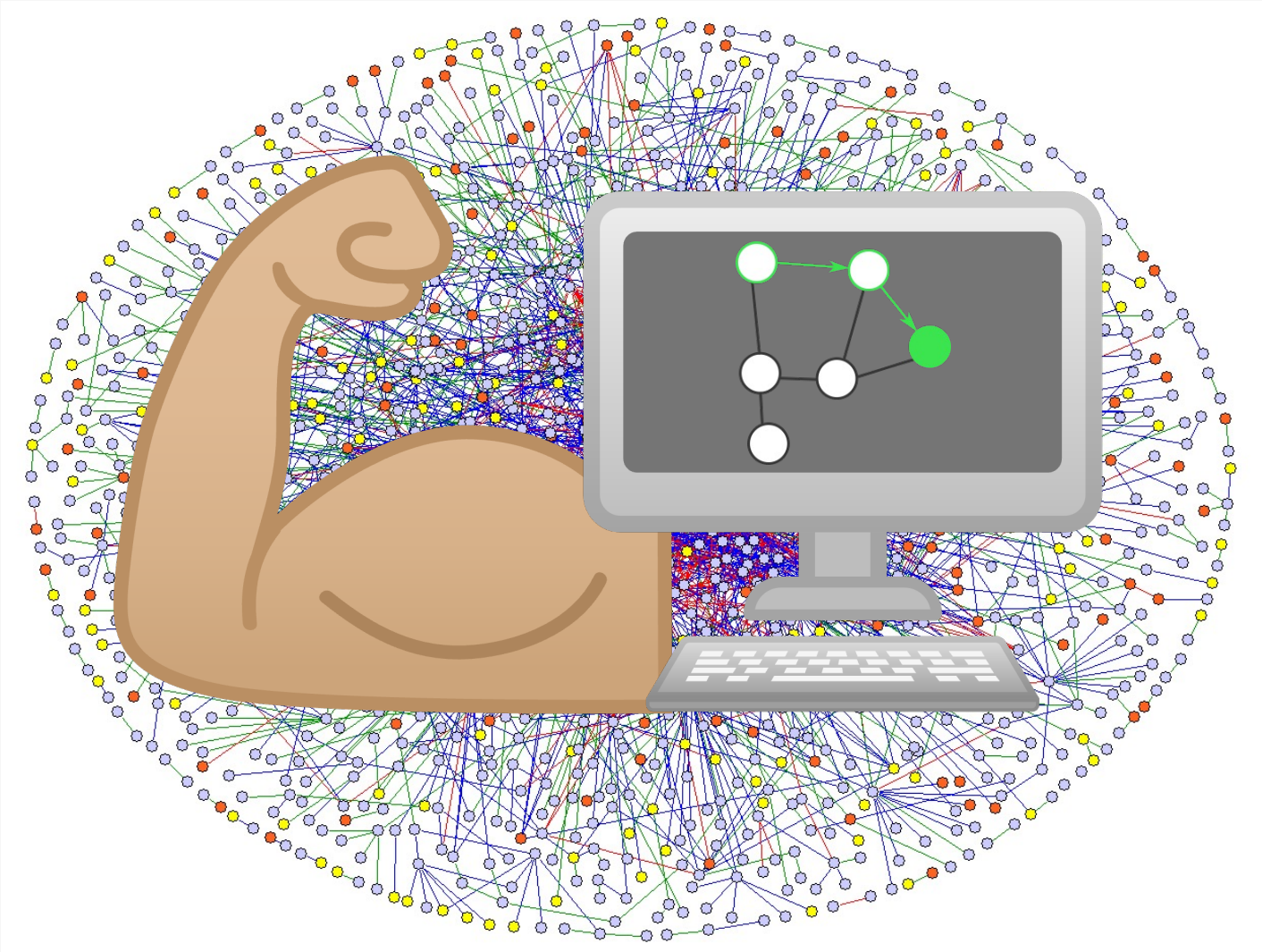


# Idea: ask computers



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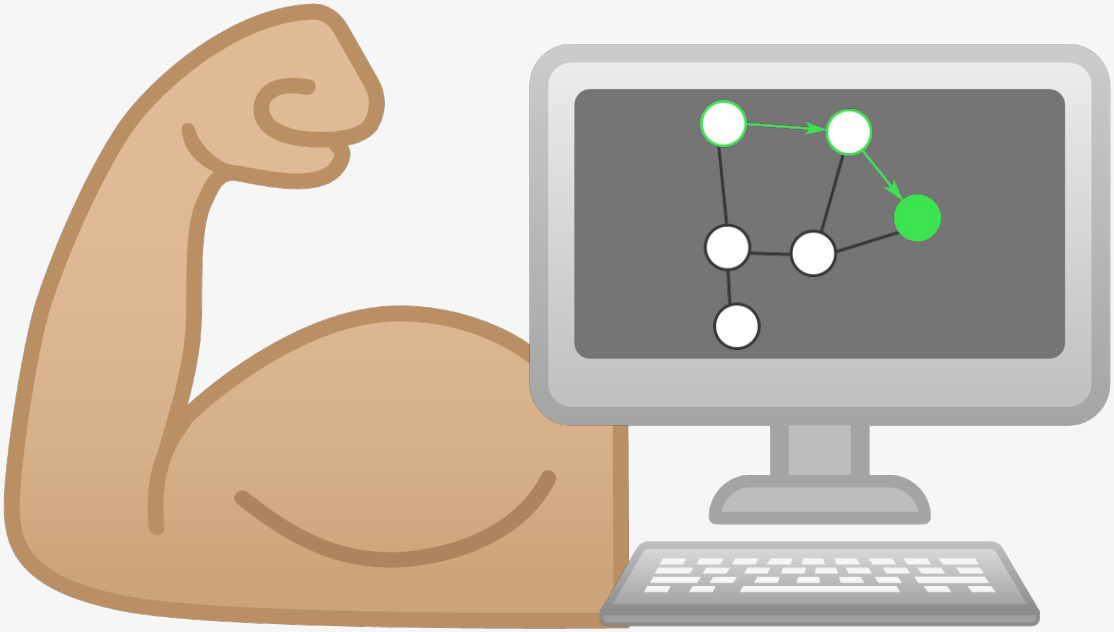
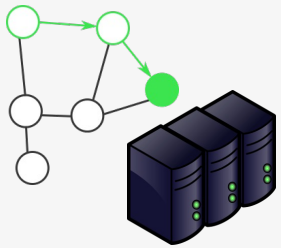


To do something, a computer needs **instructions**:
we need a **systematic description** of our problems

# Models for biology: easy, right?



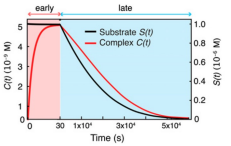
$$E + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} C \xrightarrow{k_{cat}} E + P$$

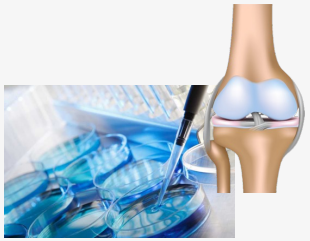
$$\frac{dE(t)}{dt} = -k_f \cdot E(t) \cdot S(t) + k_r \cdot C(t) + k_{cat} \cdot C(t)$$

$$\frac{dS(t)}{dt} = -k_f \cdot E(t) \cdot S(t) + k_r \cdot C(t)$$

$$\frac{dC(t)}{dt} = k_f \cdot E(t) \cdot S(t) - k_r \cdot C(t) - k_{cat} \cdot C(t)$$

$$\frac{dP(t)}{dt} = k_{cat} \cdot C(t)$$



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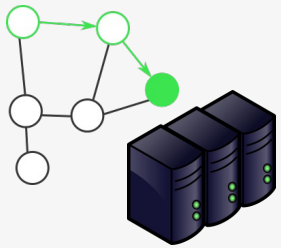
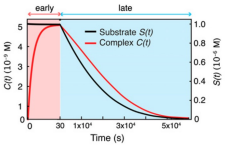
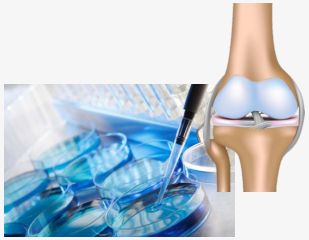


$$E + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} C \xrightarrow{k_{cat}} E + P$$

$$\begin{aligned}
\frac{dE(t)}{dt} &= -k_f \cdot E(t) \cdot S(t) + k_r \cdot C(t) + k_{cat} \cdot C(t) \\
\frac{dS(t)}{dt} &= -k_f \cdot E(t) \cdot S(t) + k_r \cdot C(t) \\
\frac{dC(t)}{dt} &= k_f \cdot E(t) \cdot S(t) - k_r \cdot C(t) - k_{cat} \cdot C(t) \\
\frac{dP(t)}{dt} &= k_{cat} \cdot C(t)
\end{aligned}$$



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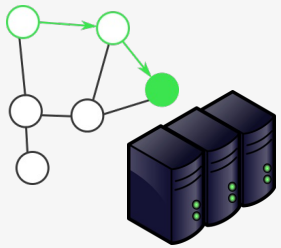

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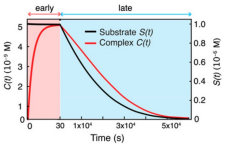
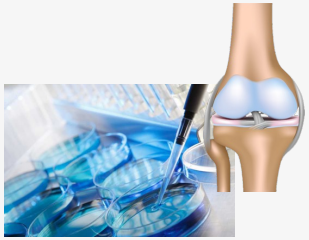
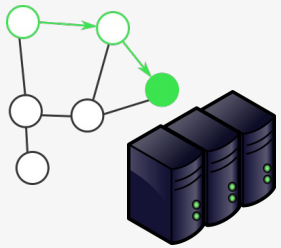
$$\frac{dP(t)}{dt} = k_{cat} \cdot C(t)$$



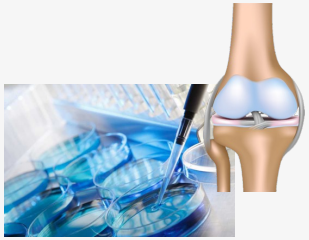



*Lesson #2: terminology*

# Formal models

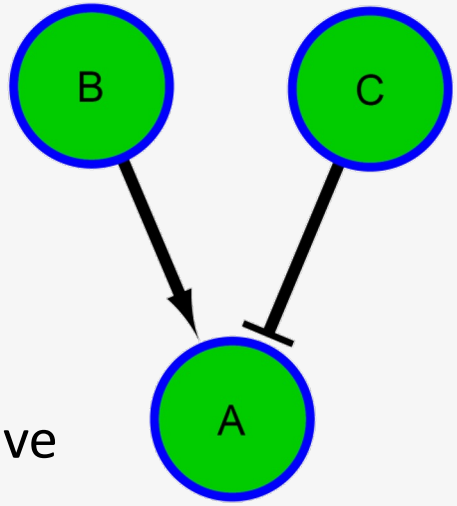


No, we mean
*formal* models



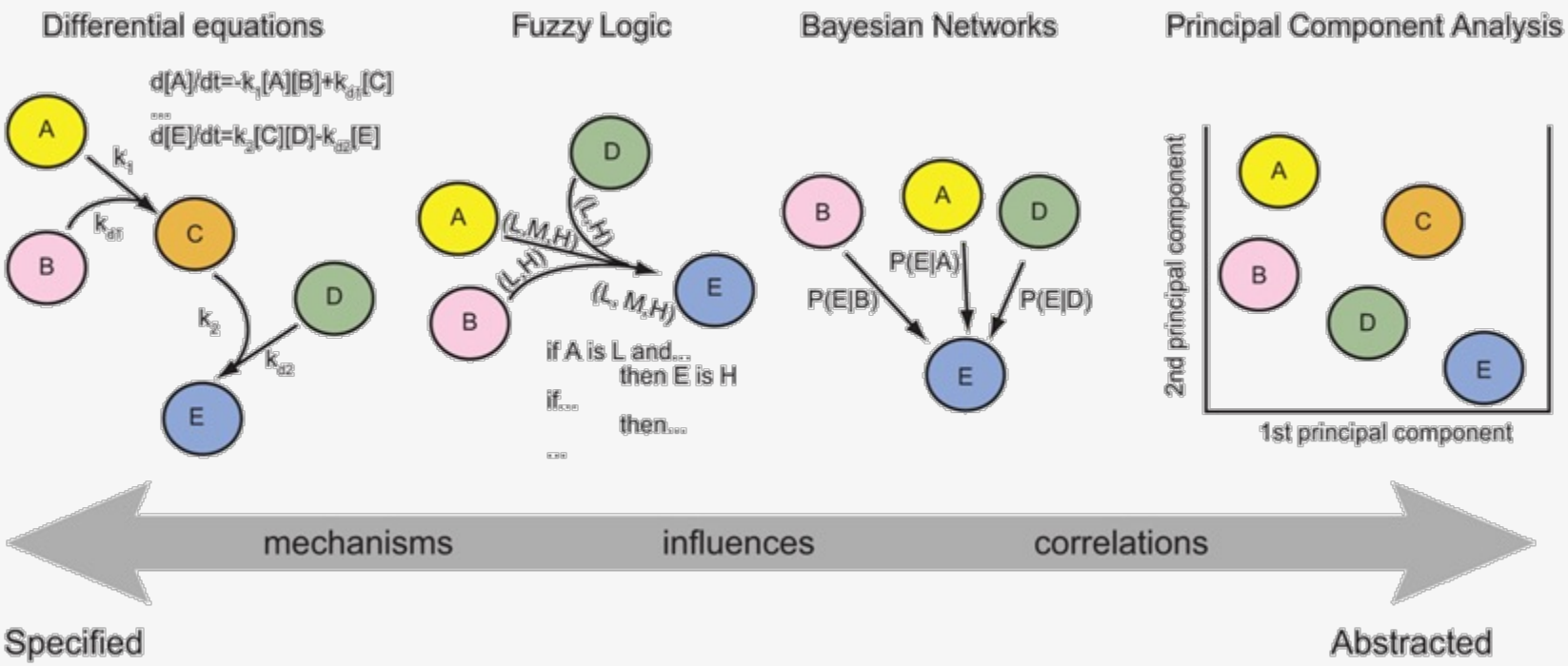
# Formal models to understand complex biological netwoks

Formal model = Precise description of knowledge

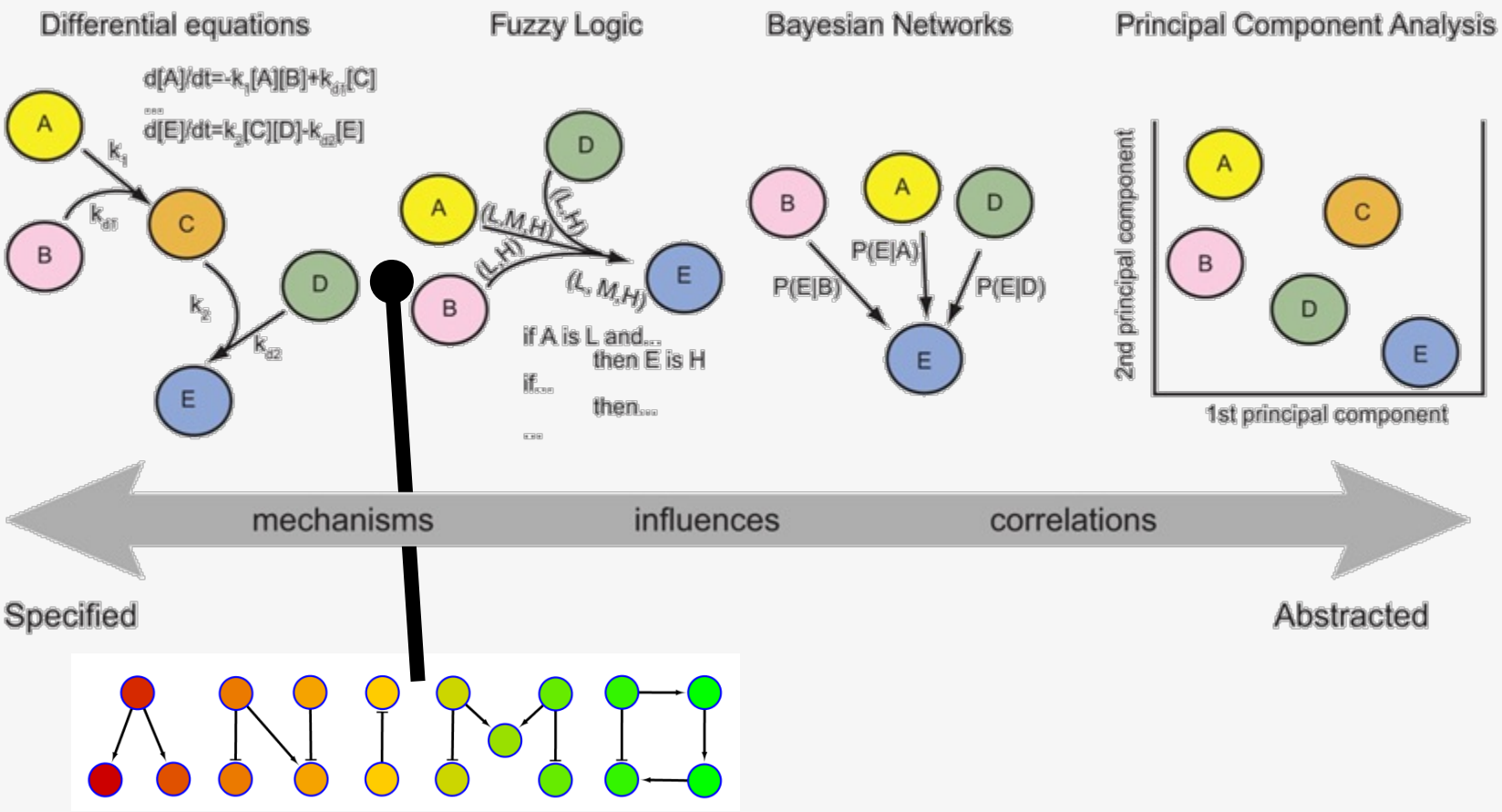



- Logic:
  - **IF** B is active **AND** C is **NOT** active, **THEN** A is active
- Mathematical equation (ODE):
  - $\frac{d[A]}{dt} = k_1[B] - k_2[C] - k_3[A]$

# Models range: mechanistic → abstract



# Models range: mechanistic → abstract



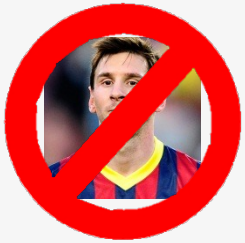

**Modelling with ANIMO: between fuzzy logic and differential equations.**
S. Schivo, J. Scholma, P.E. van der Vet, H.B.J. Karperien, J.N. Post, J.C. van de Pol, R. Langerak.
In: BMC systems biology, Vol. 10, 27.07.2016, p. 56.

# Modelling software: what biologists want

- Intuitive
  - Hidden mathematics
  - Visual interface
- Interactive
  - Adaptable
  - Rapid feedback

# Modelling software: what biologists want

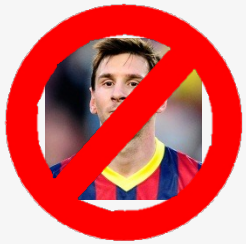
- Intuitive
  - Hidden mathematics
  - Visual interface

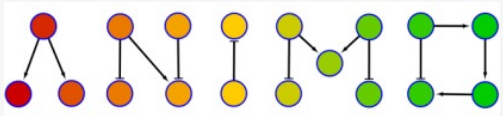


- Interactive
  - Adaptable
  - Rapid feedback

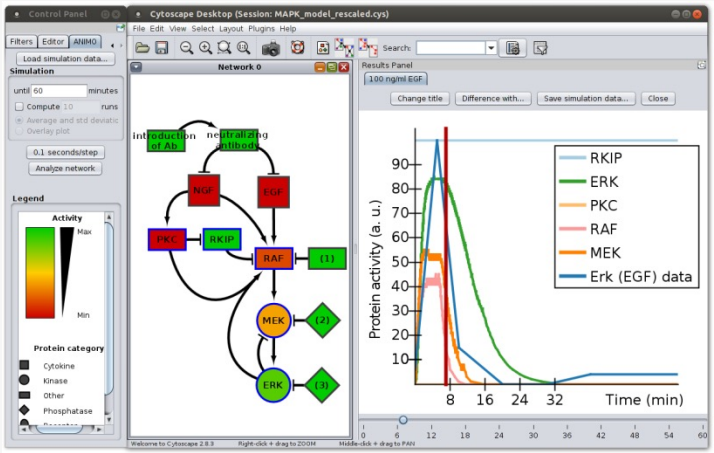
# Modelling software: what biologists want

- Intuitive
  - Hidden mathematics
  - Visual interface





- Interactive
  - Adaptable
  - Rapid feedback



# Why not precise?

***Why publishing in multidisciplinary journals can be a pain…***

# Why not precise?

***Why publishing in multidisciplinary journals can be a pain…***

We need to know why this is precise

We don’t care about those details

# Why not precise?

## *Why publishing in multidisciplinary journals can be a pain…*

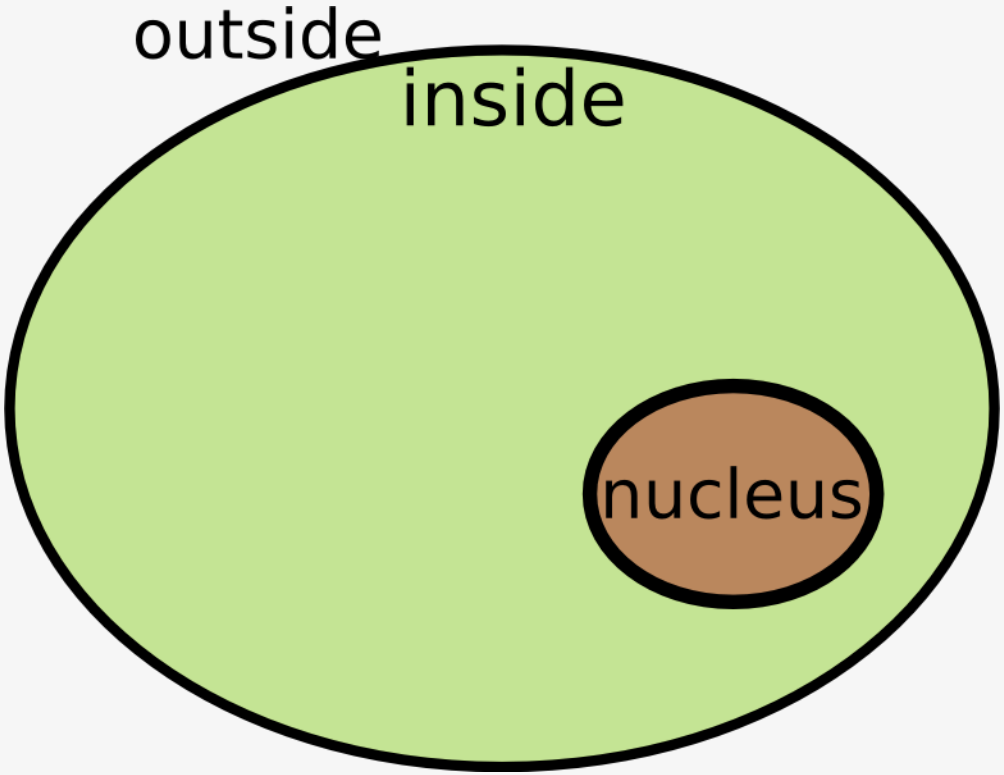
We need to know why this is precise

*We can and want to be precise*
*(a bit of Dunning-Kruger effect)*

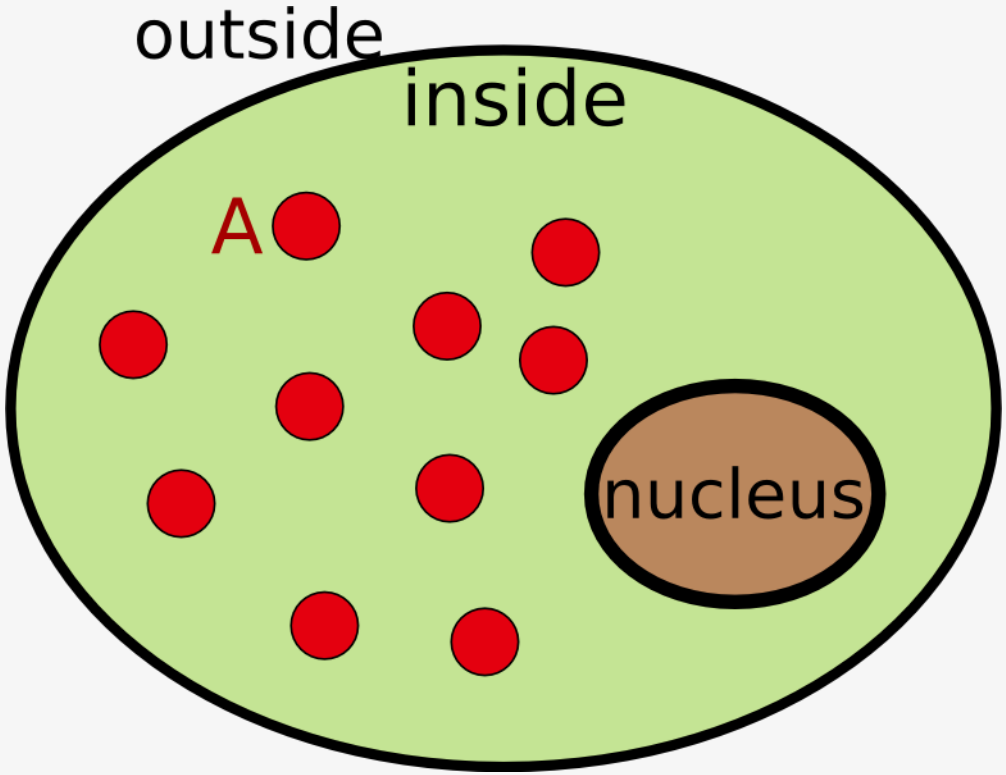
We don't care about those details

*We are unable to be precise:*
*most parameters are hard to measure*

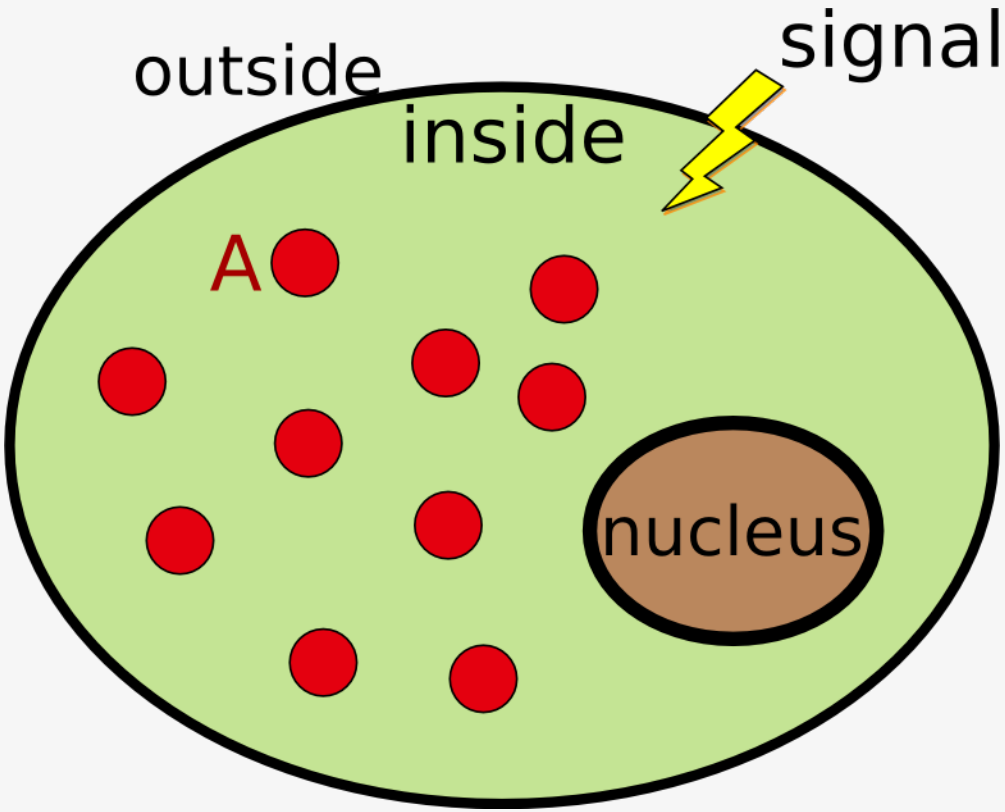
# Abstractions: activity levels



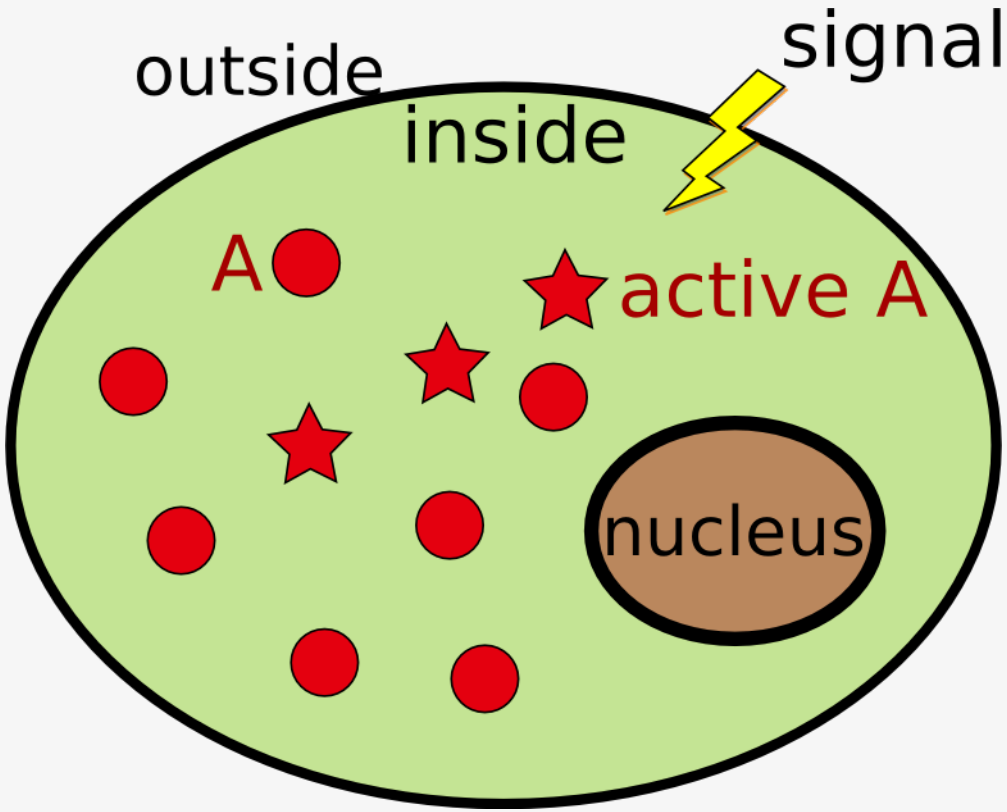
# Abstractions: activity levels



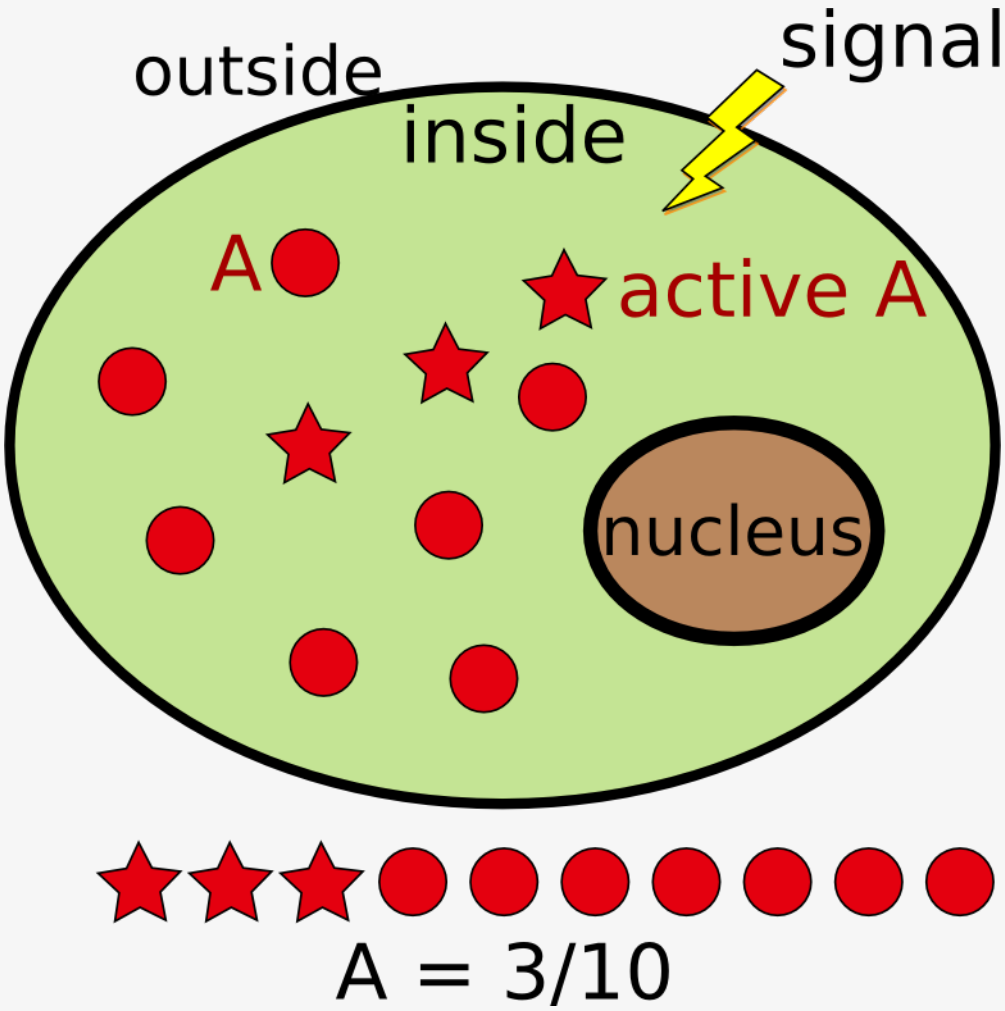
# Abstractions: activity levels



# Abstractions: activity levels



# Abstractions: activity levels



# Abstractions: interactions

Precise reactions → abstract *interactions*

$$E + S + ATP \rightleftarrows ES + ATP \rightarrow ES^P + ADP \rightleftarrows E + S^P + ADP$$

$$(\text{with } S + S^P = \text{constant and } ATP + ADP = \text{constant})$$

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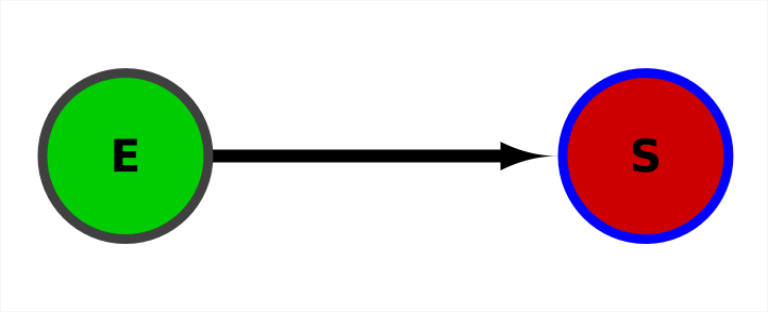
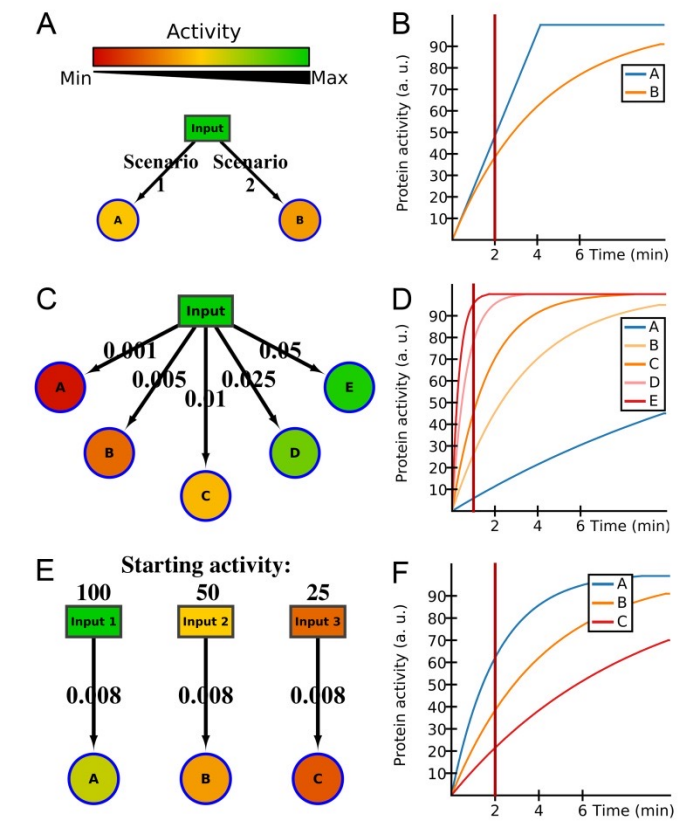
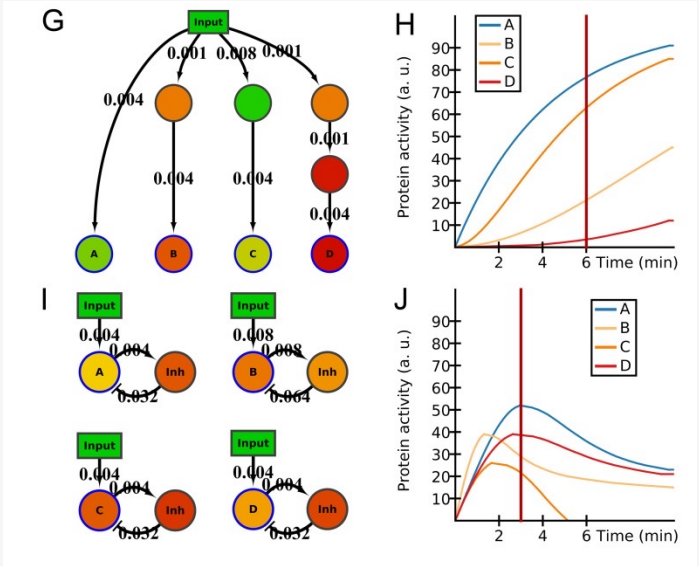


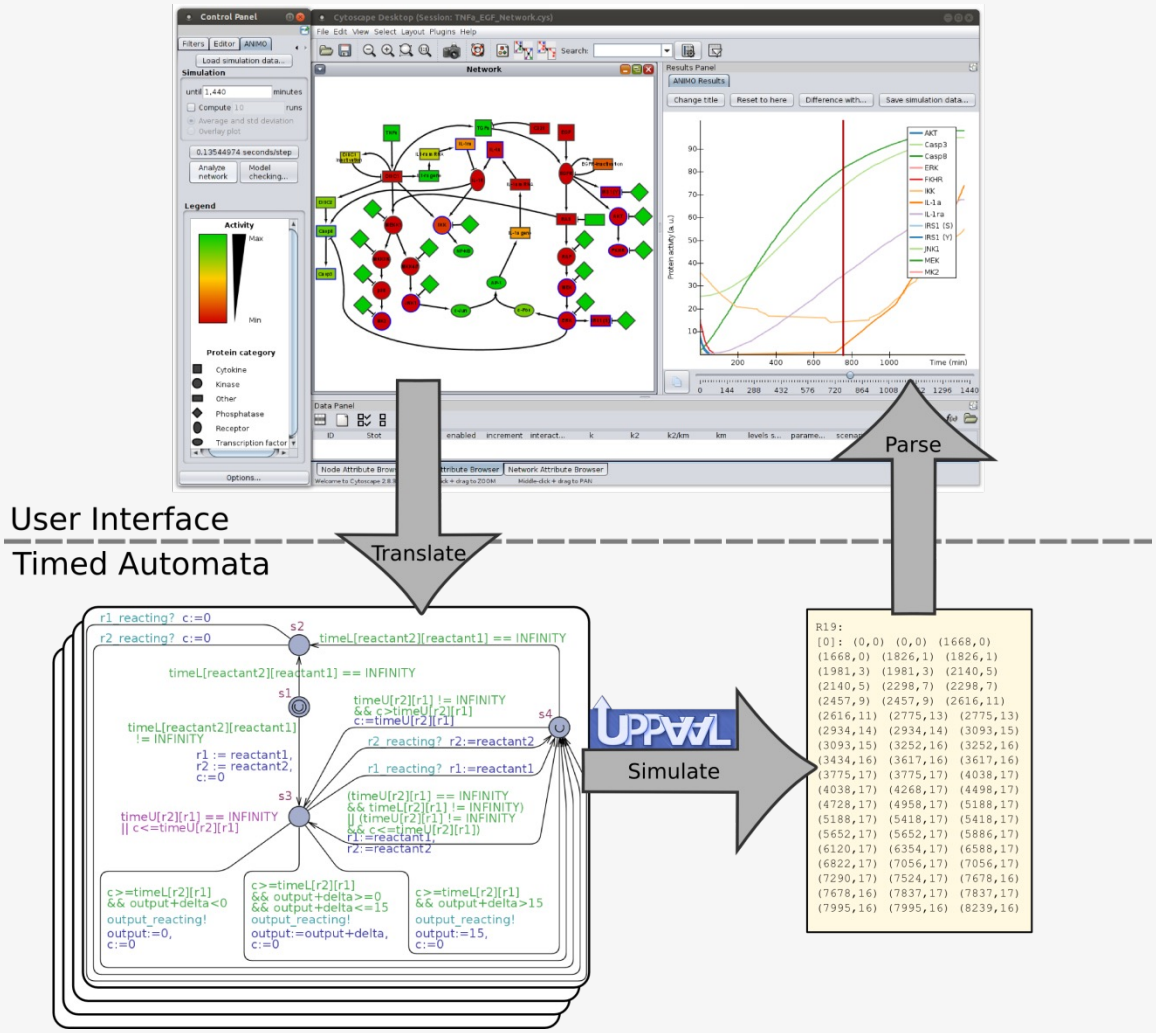
# Abstractions: interactions




**Biological networks 101: computational modeling for molecular biologists.**
J. Scholma, S. Schivo, R.A. Urquidi Camacho, J.C. van de Pol, H.B.J. Karperien, J.N. Post.
In: Gene, Vol. 533, No. 42, 01.01.2014, p. 379-384.

# ANIMO: under the hood

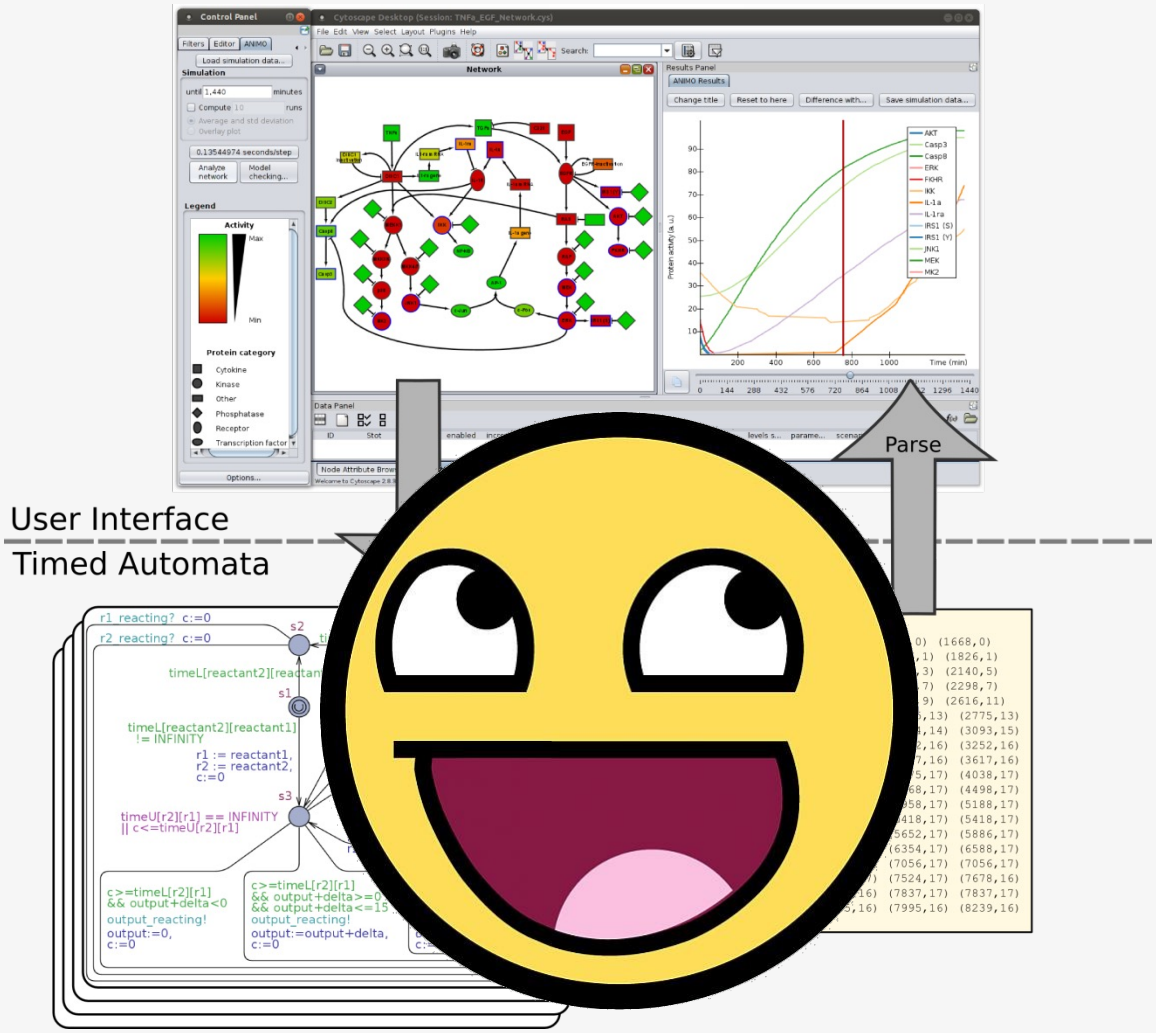




Schivo et al. (2014). *Modeling biological pathway dynamics with Timed Automata.*

Schivo et al. (2016). *Modelling with ANIMO: between fuzzy logic and differential equations.*

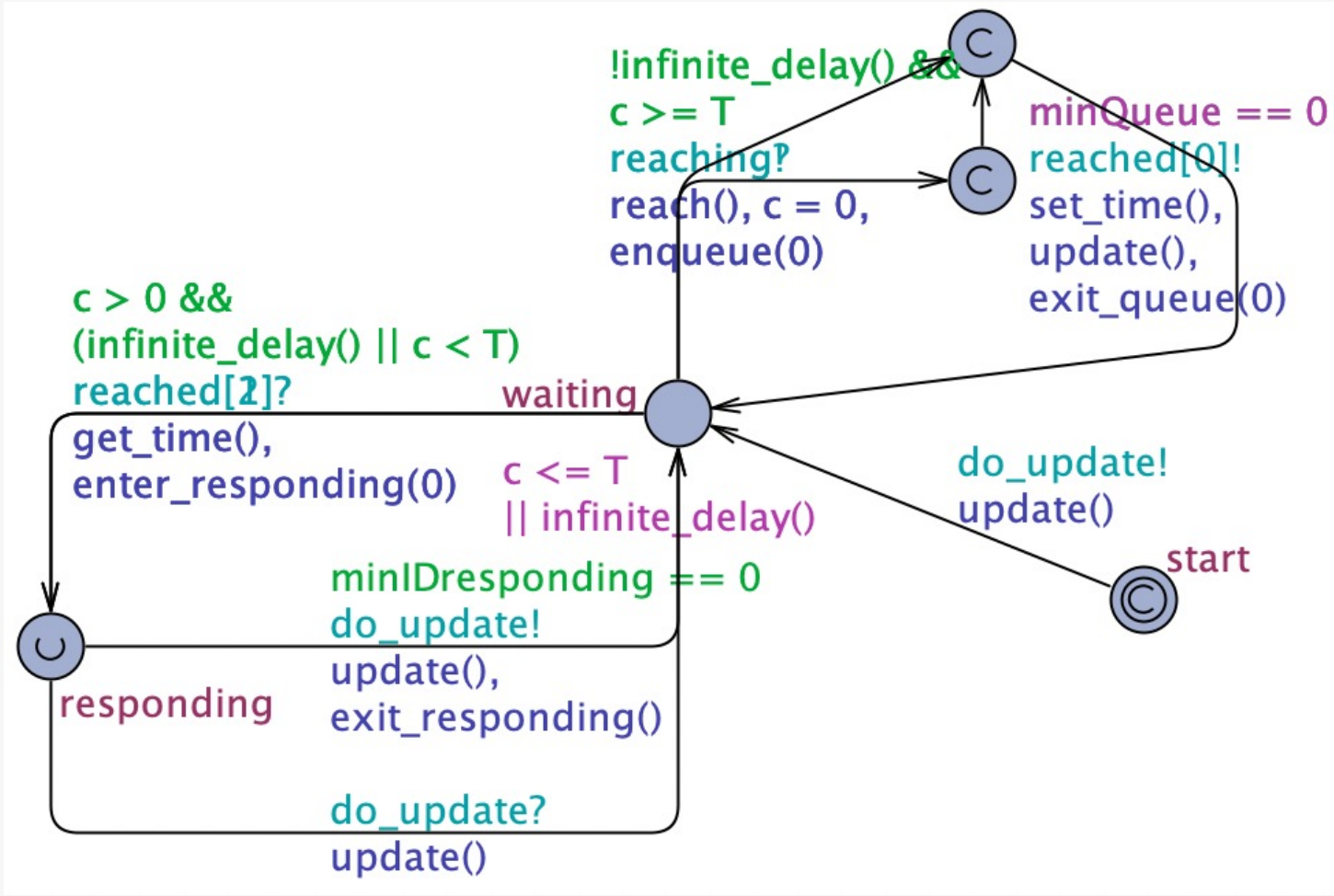
# ANIMO: under the hood




Schivo et al. (2014). *Modeling biological pathway dynamics with Timed Automata.*

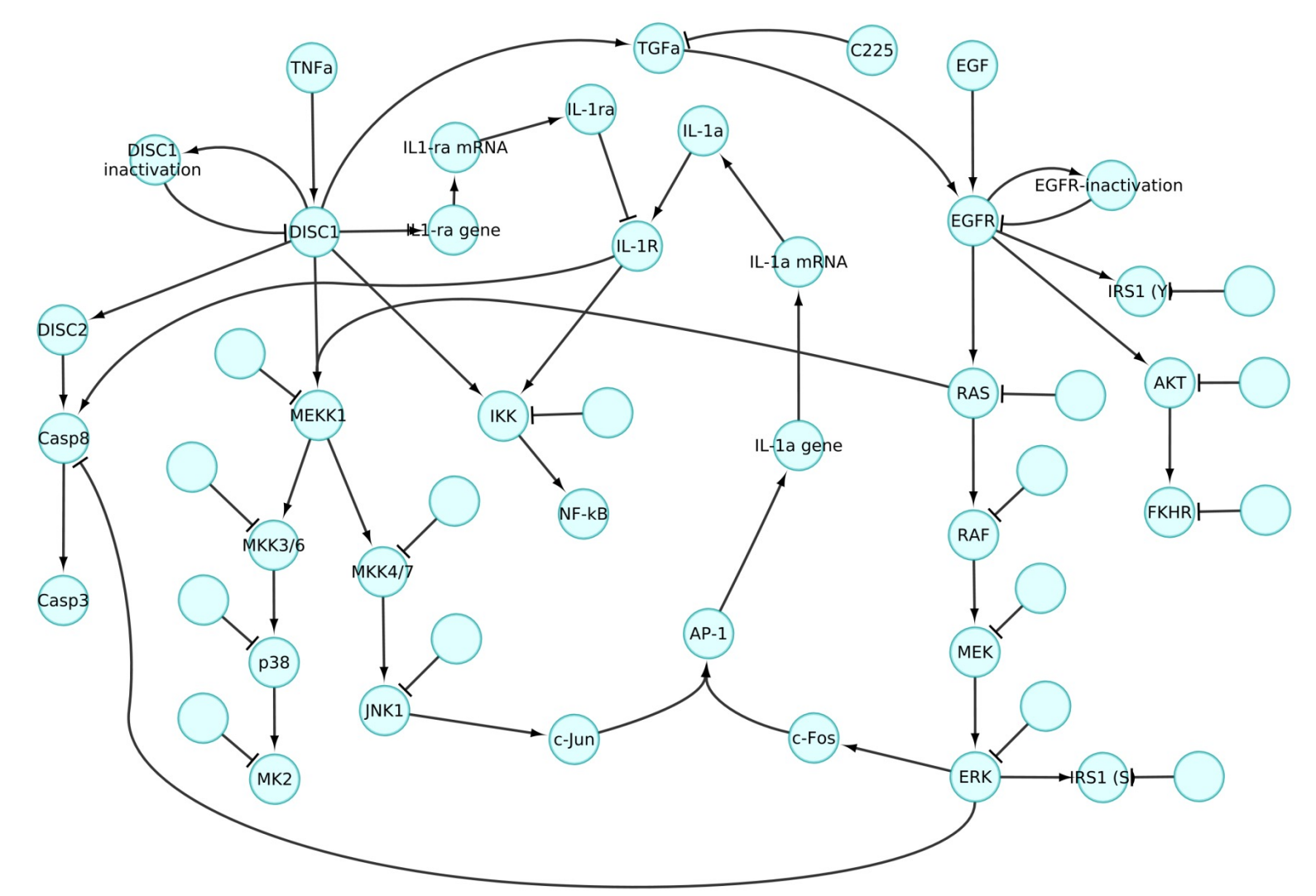
Schivo et al. (2016). *Modelling with ANIMO: between fuzzy logic and differential equations.*

# ANIMO model

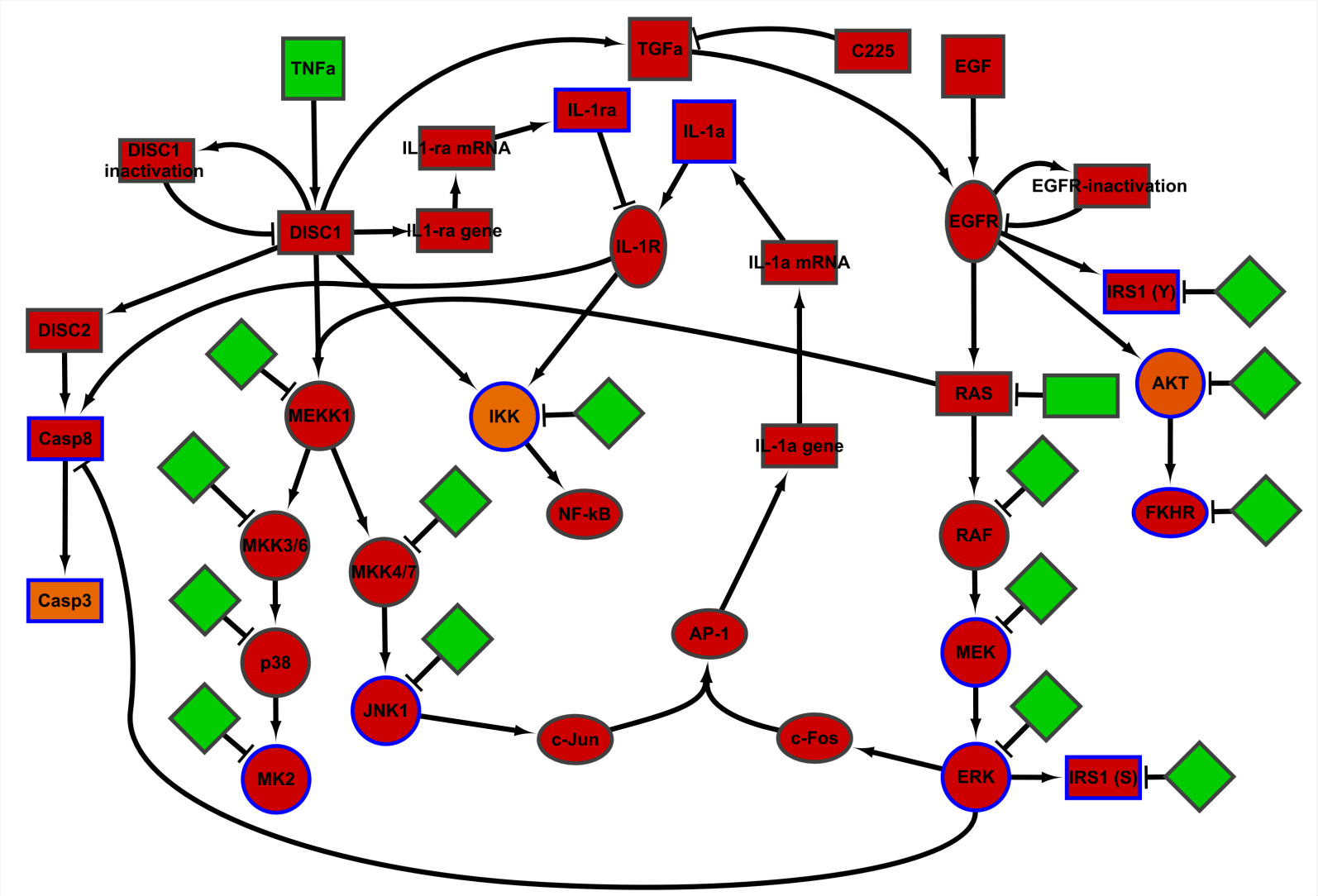



Schivo & Langerak (2017). *Discretization of continuous dynamical systems using UPPAAL.*

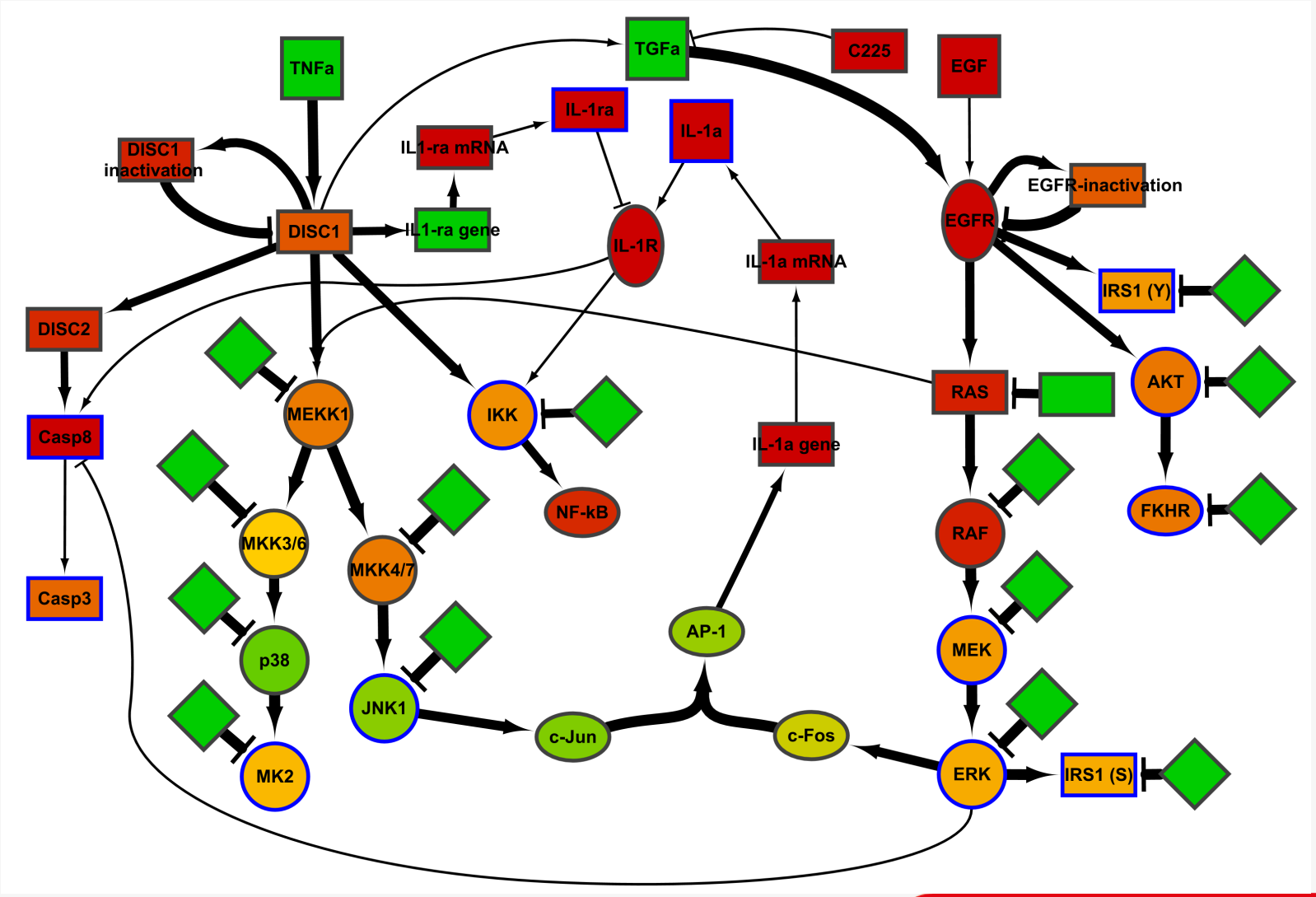
# ANIMO workflow



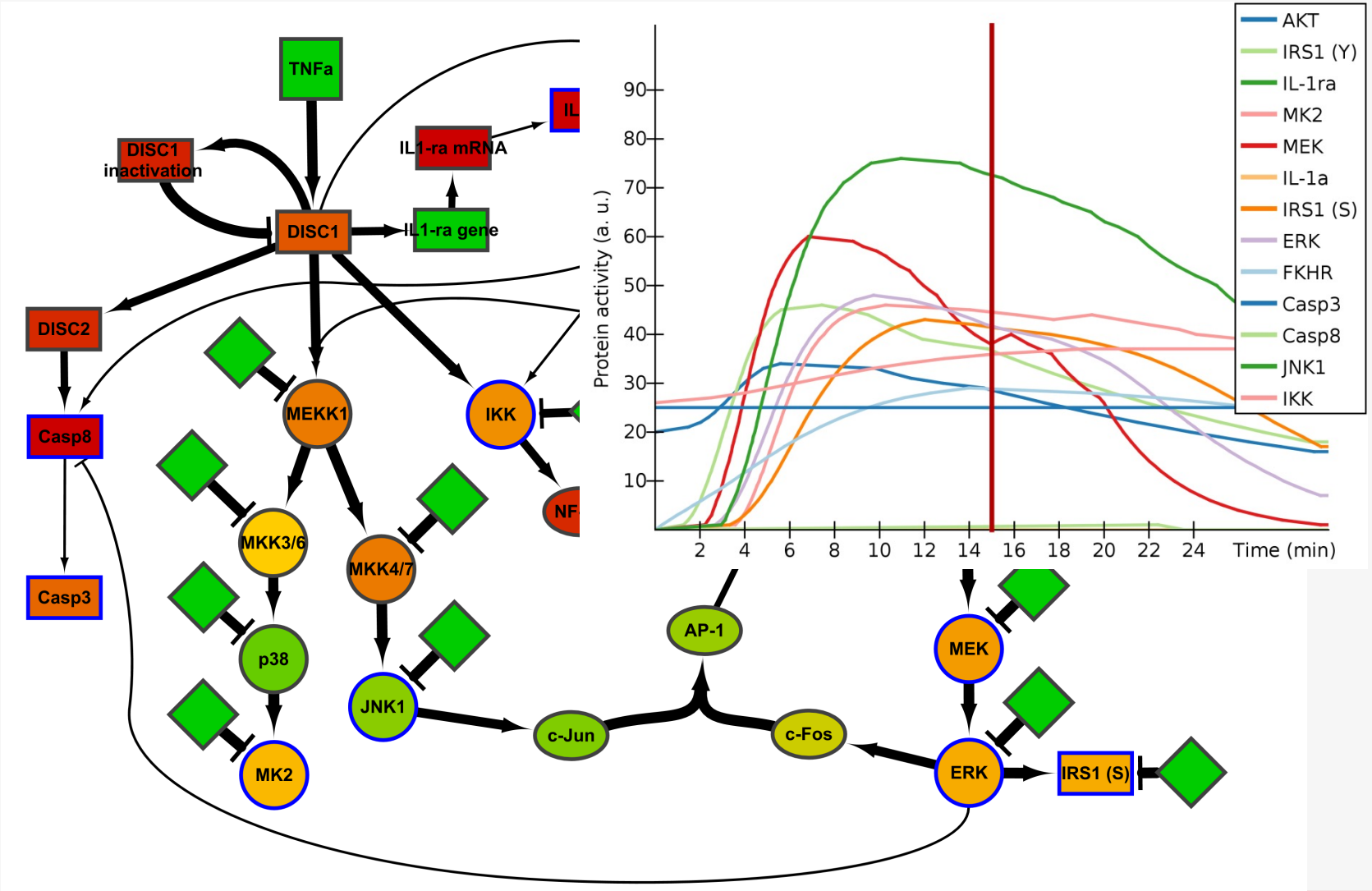
# ANIMO workflow



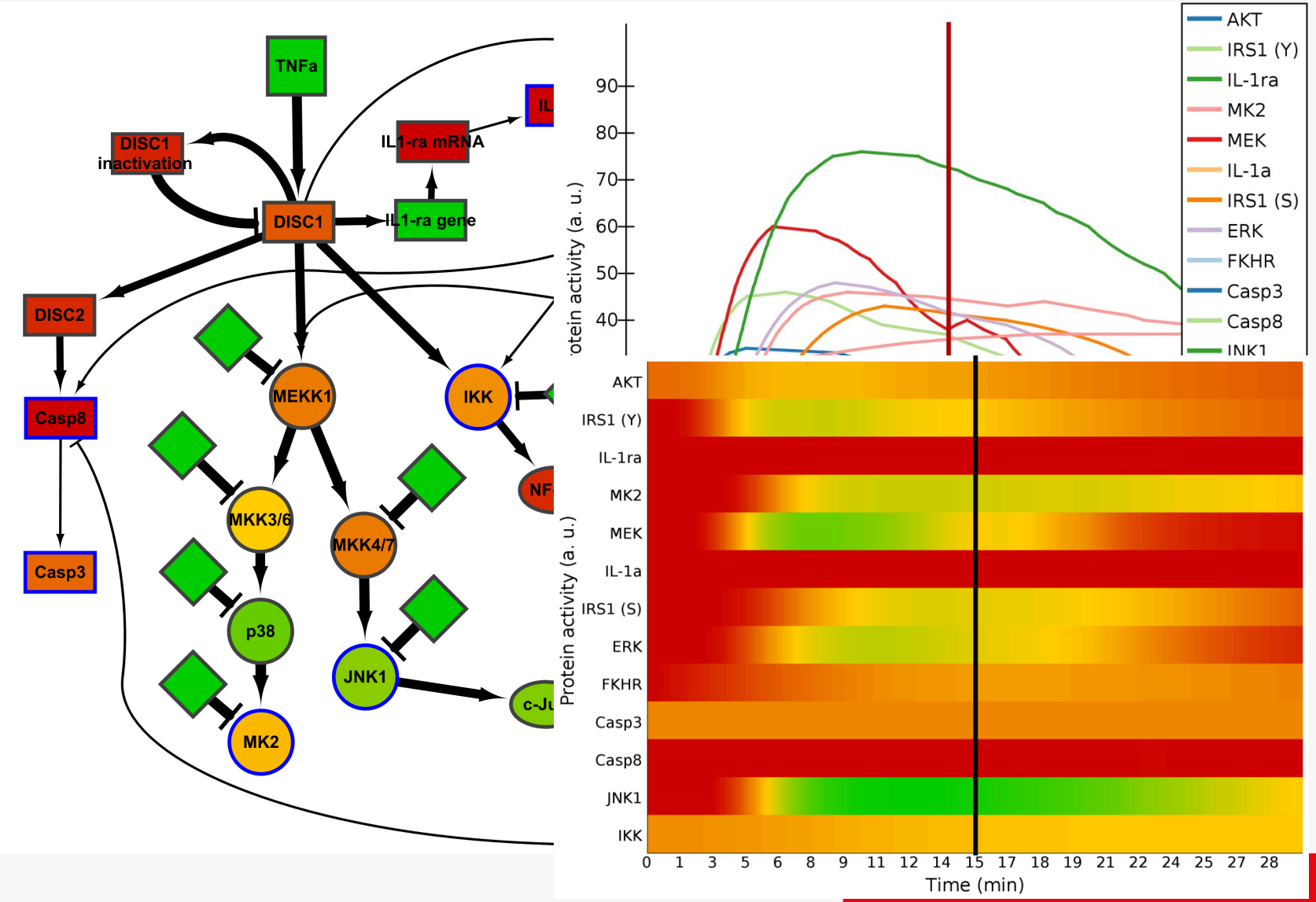
# ANIMO workflow



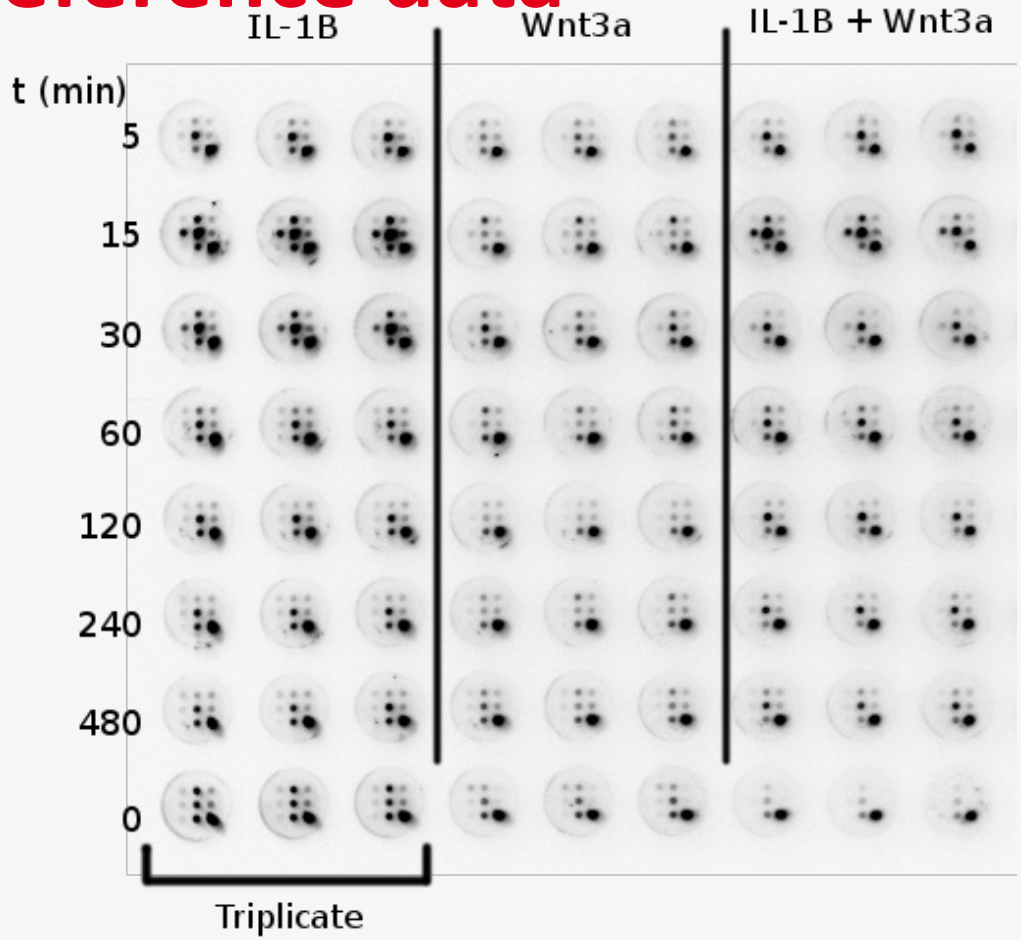
# ANIMO workflow



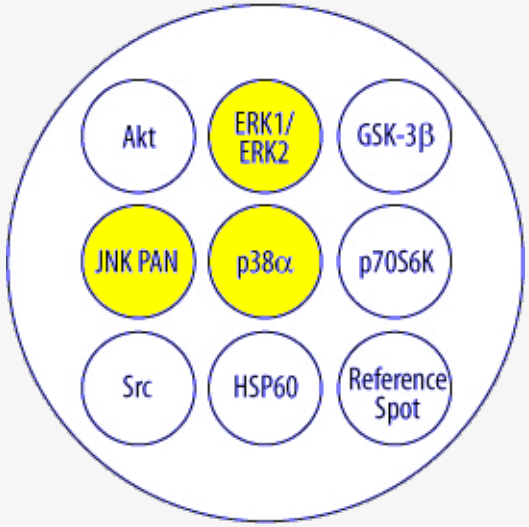
# ANIMO workflow



# Reference data



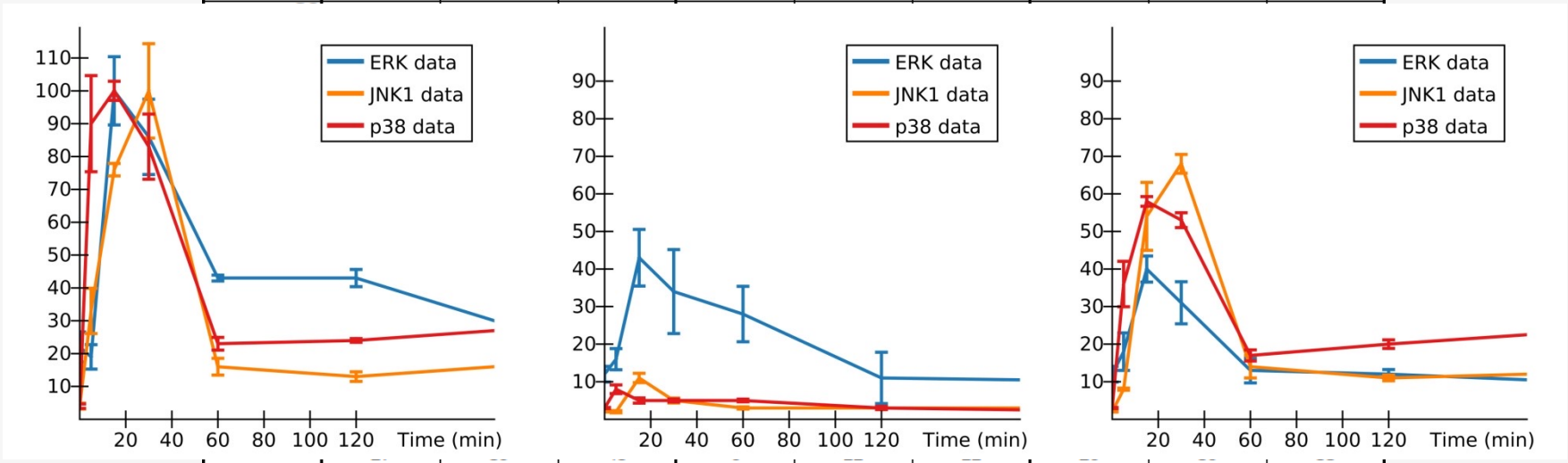

**Biological networks 101: computational modeling for molecular biologists.** / J. Scholma, S. Schivo, R.A. Urquidi Camacho, J.C. van de Pol, H.B.J. Karperien, J.N. Post. In: Gene, Vol. 533, No. 42, 01.01.2014, p. 379-384.




(Relative phosphorylation values of proteins in human chondrocytes)
Time series measure the dynamic evolution of signal.

# Reference data

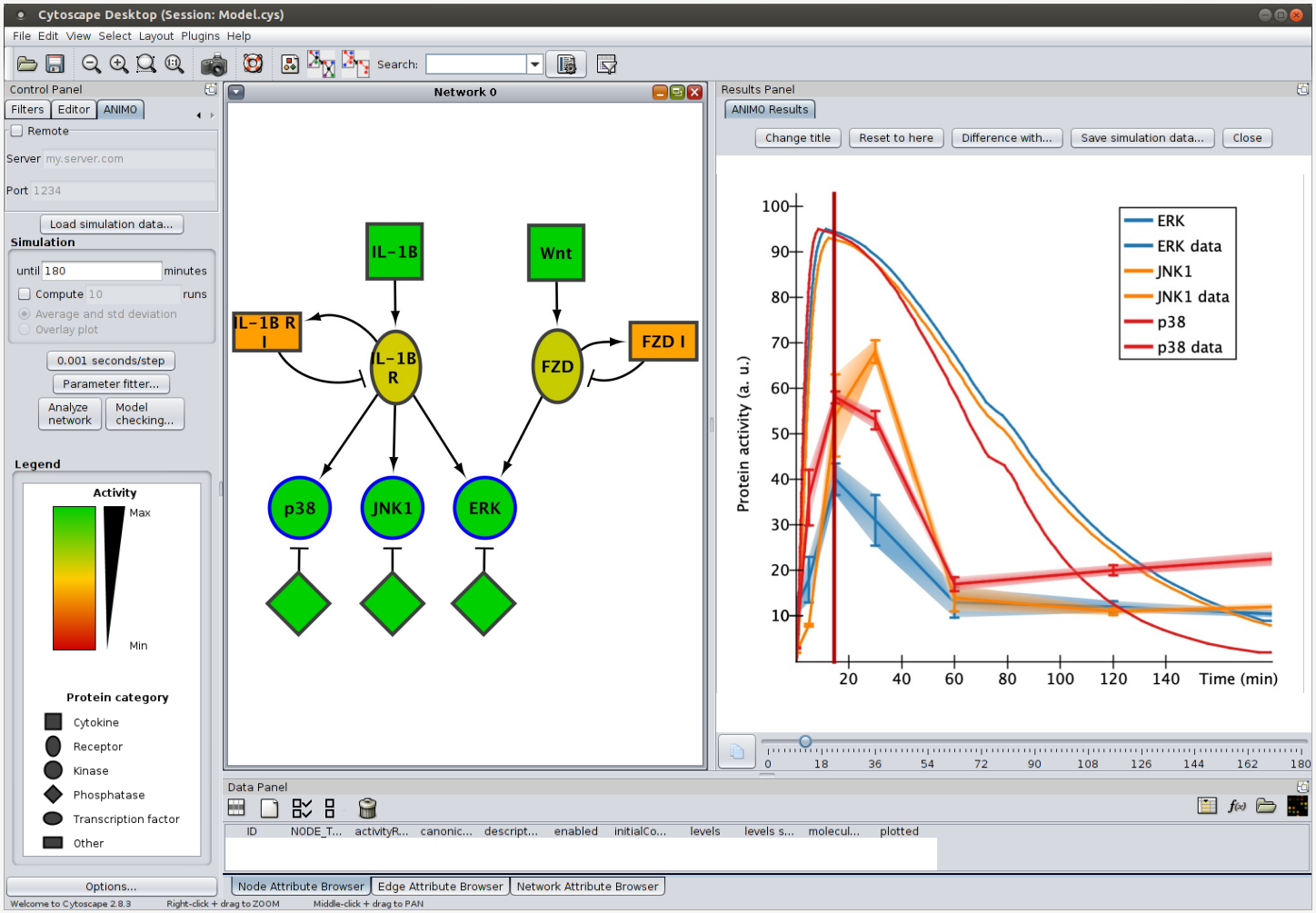
| | IL-1β | | | Wnt 3a | | | IL-1β + Wnt 3a | | |
|---|---|---|---|---|---|---|---|---|---|
| ERK | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 5 | 13 | 18 | 17 | 15 | 15 | 21 | 11 | 14 | 12 |
| 15 | 82 | 90 | 108 | 42 | 46 | 51 | 53 | 59 | 27 |
| 30 | 45 | 65 | 57 | 30 | 27 | 30 | 11 | 10 | 9 |




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 15 | 91 | 87 | 130 | 6 | 4 | 5 | 81 | 70 | 39 |
| 30 | 73 | 75 | 105 | 21 | 12 | 19 | 26 | 24 | 19 |
| 60 | 25 | 26 | 24 | 6 | 3 | 11 | 24 | 23 | 20 |
| 120 | 28 | 27 | 24 | 2 | 1 | 2 | 31 | 36 | 21 |
| 240 | 21 | 19 | 20 | 2 | 2 | 3 | 22 | 19 | 19 |
| 480 | 16 | 16 | 27 | 10 | 4 | 6 | 16 | 15 | 17 |
| 0 | 17 | 19 | 15 | | | | | | |

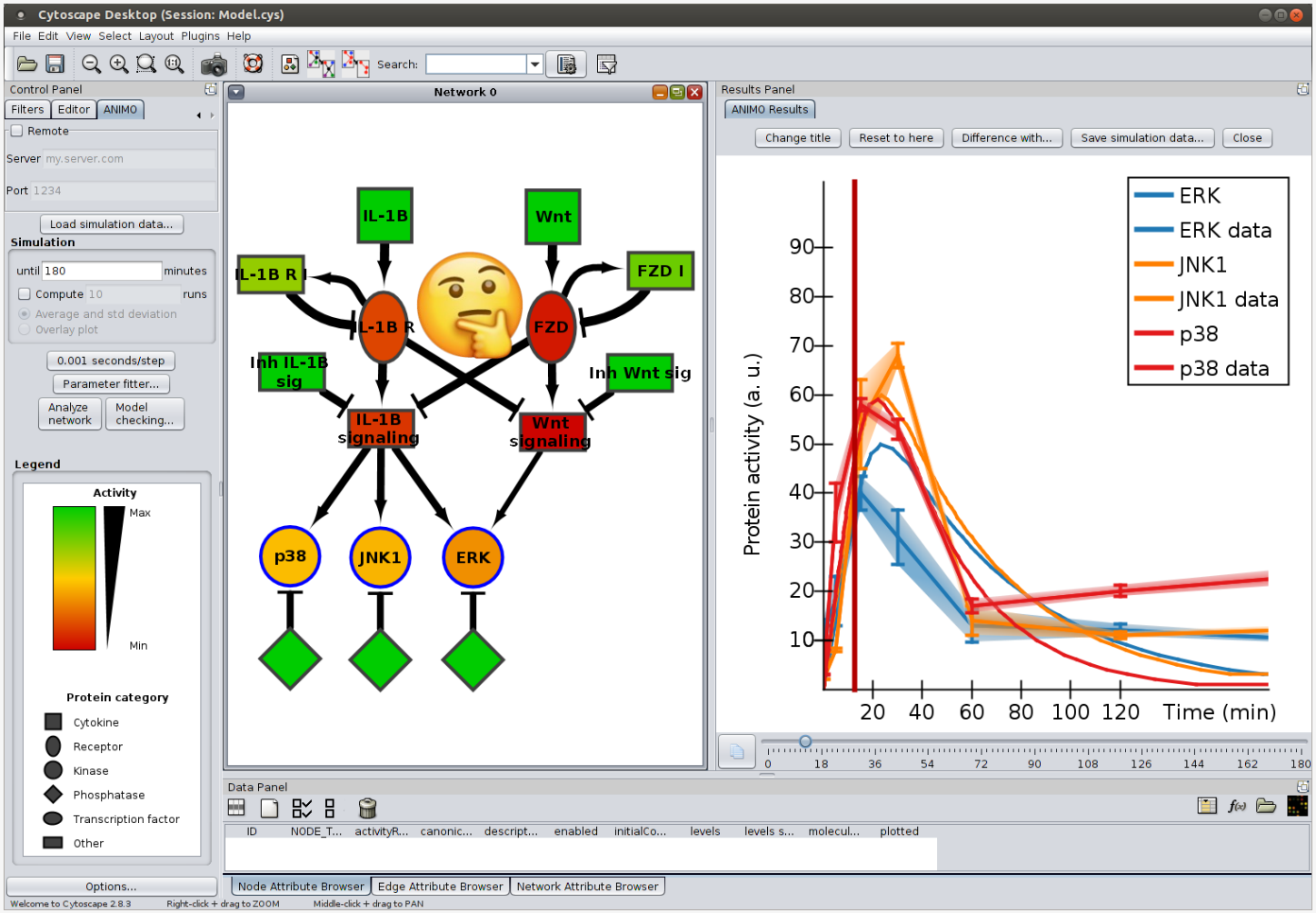
Numeric semi-quantitative data.

# Data vs Model: hypotheses



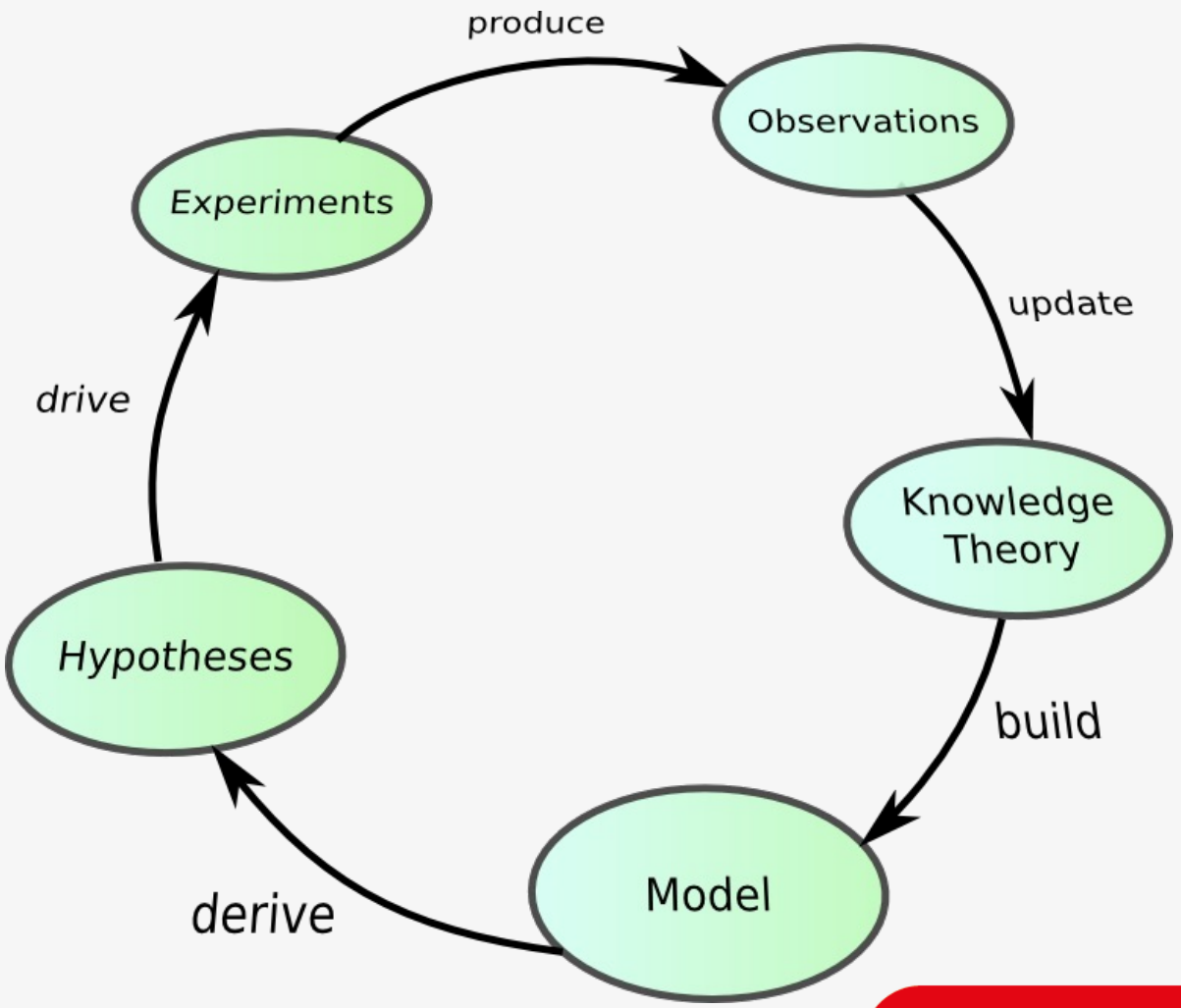

Use data and model to improve knowledge, generate hypotheses.

# Data vs Model: hypotheses

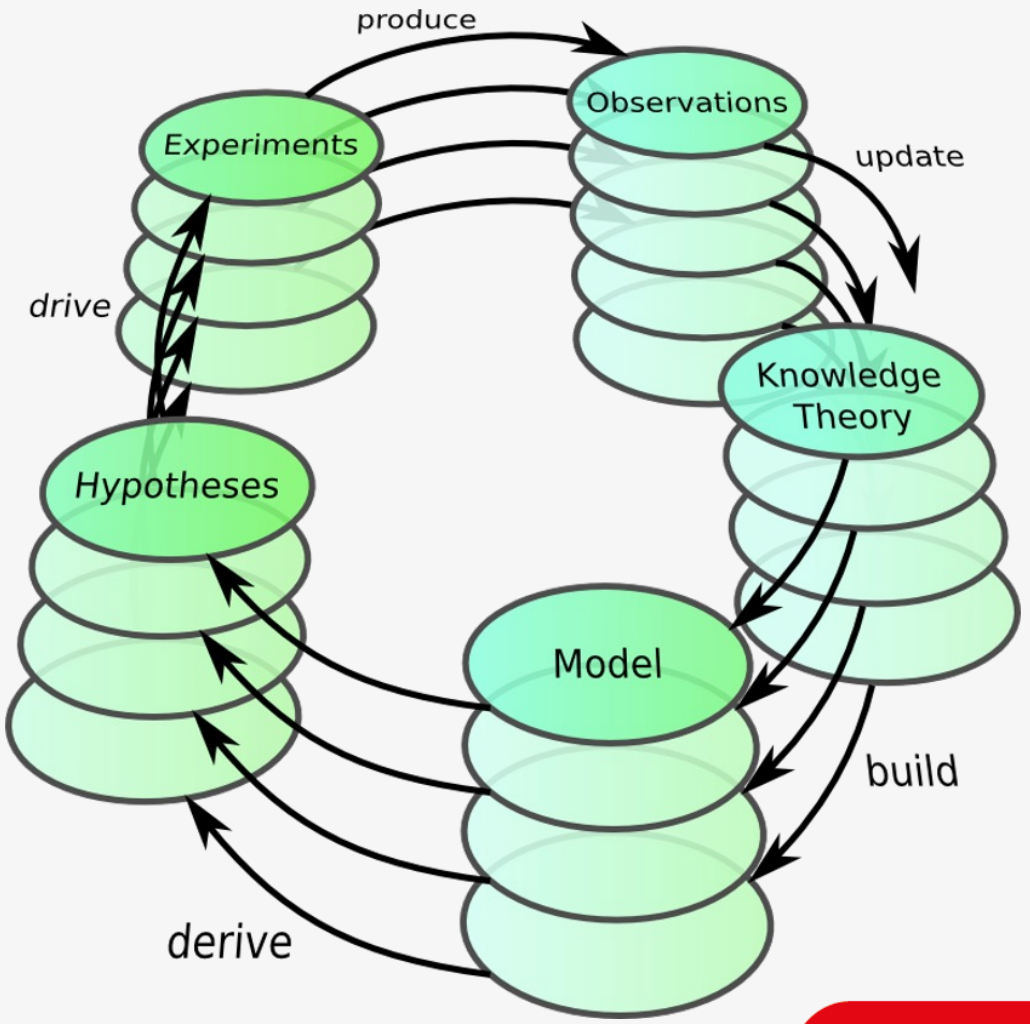



Use data and model to improve knowledge, generate hypotheses.

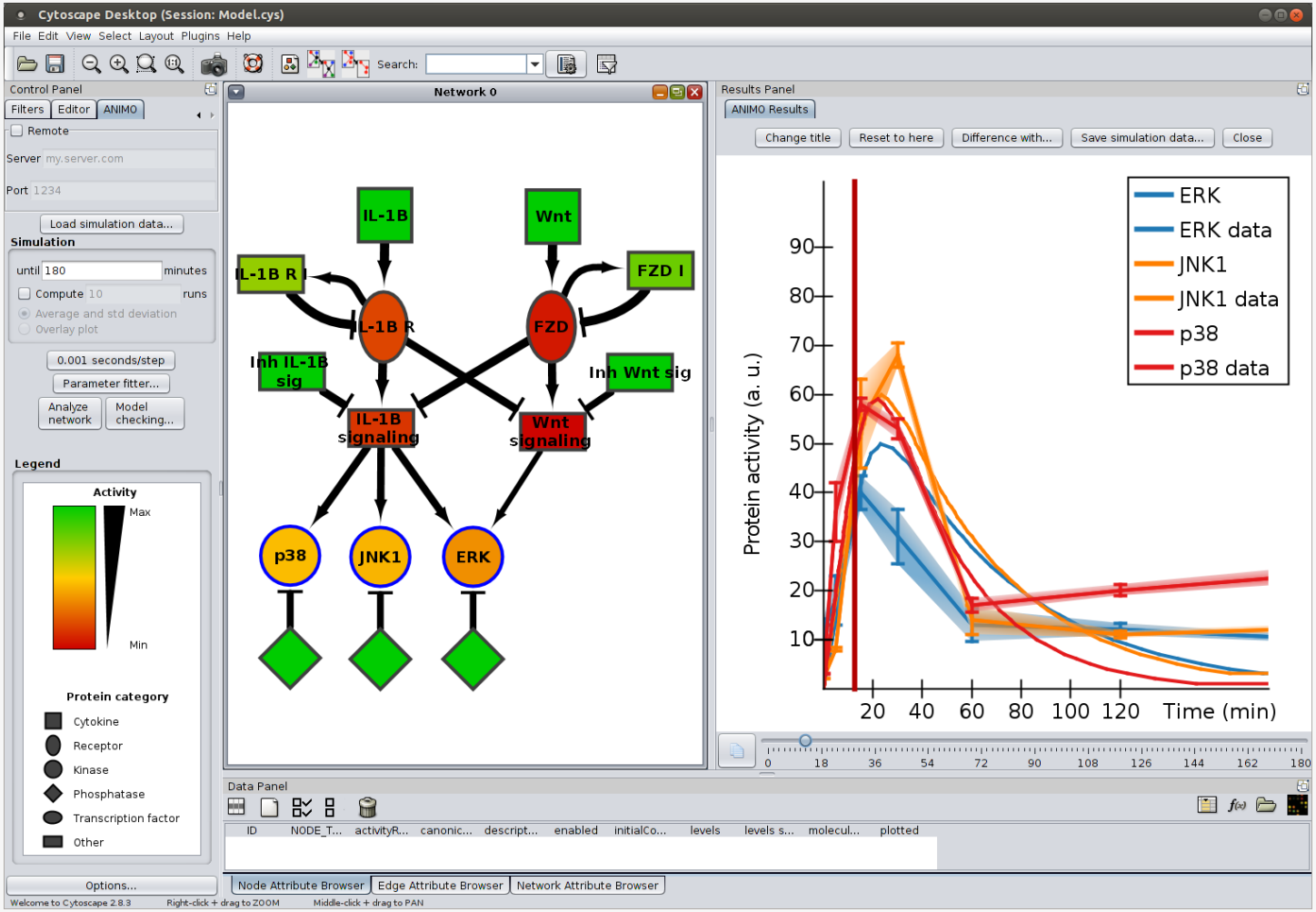
# Models in Systems Biology: the Empirical Cycle



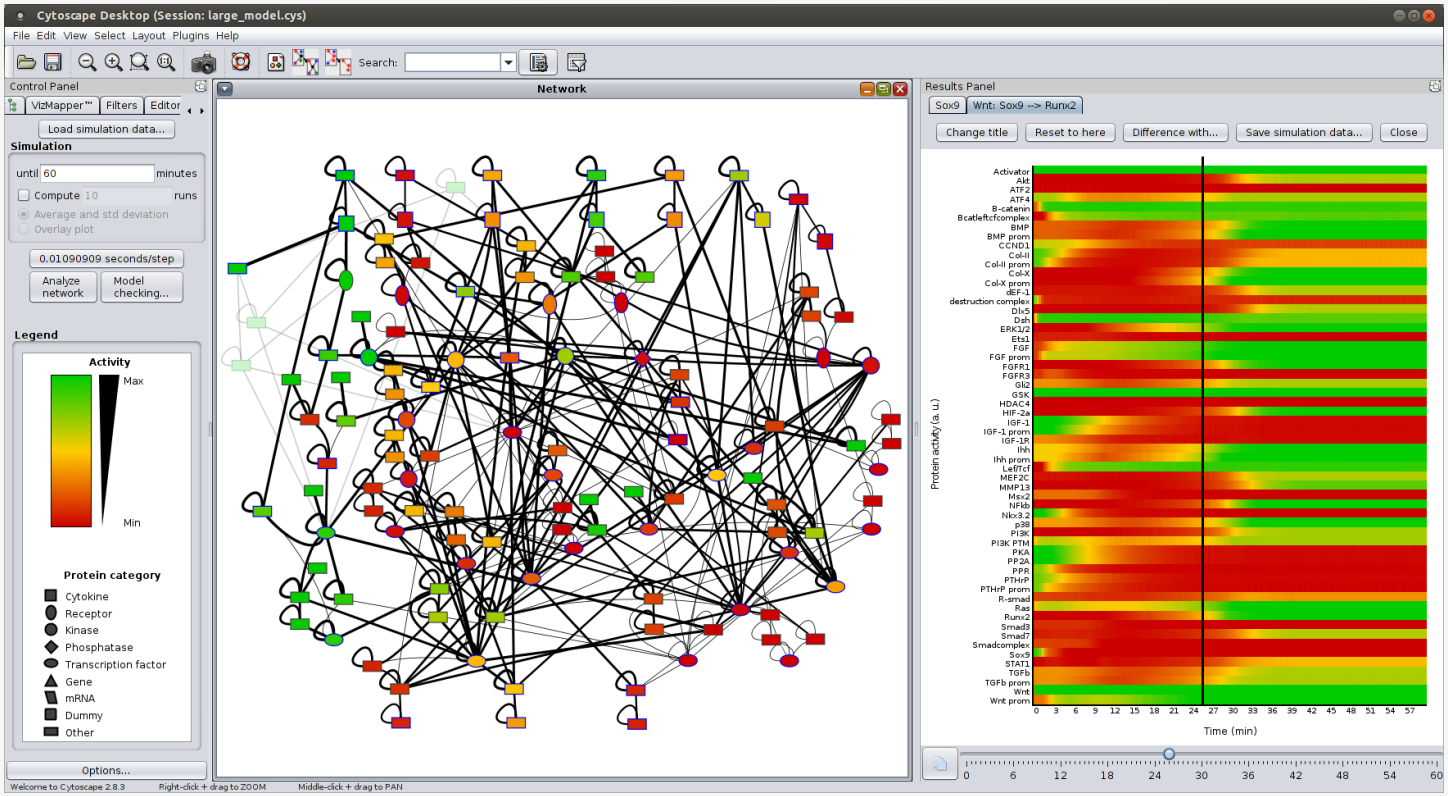
# Models in Systems Biology: the Empirical ~~Cycle~~ Spiral



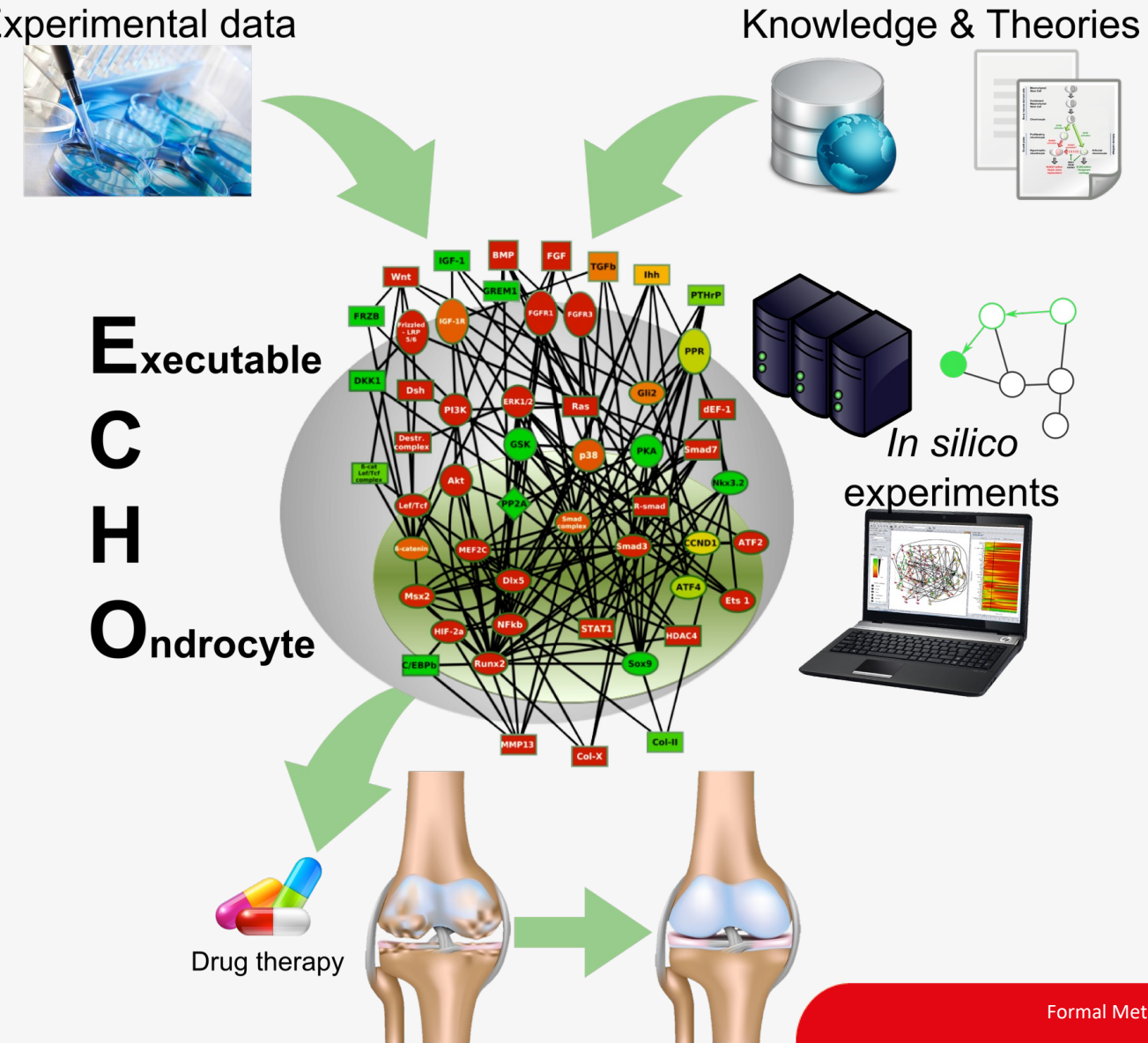
# Lesson #3: start small…



# … you can go for bigger things later on



# ECHO: Executable CHOndrocyte



# ECHO: Executable CHOndrocyte

ELSEVIER

Cellular Signalling

Volume 68, April 2020, 109471

## ECHO, the executable CHOndrocyte: A computational model to study articular chondrocytes in health and disease

Stefano Schivo [a, b, c], Sakshi Khurana [a, 1], Kannan Govindaraj [a, 1], Jetse Scholma [a], Johan Kerkhofs [d, e], Leilei Zhong [a, f], Xiaobin Huang [a], Jaco van de Pol [b, g], Rom Langerak [b], André J. van Wijnen [h], Liesbet Geris [d], Marcel Karperien [a], Janine N. Post [a]

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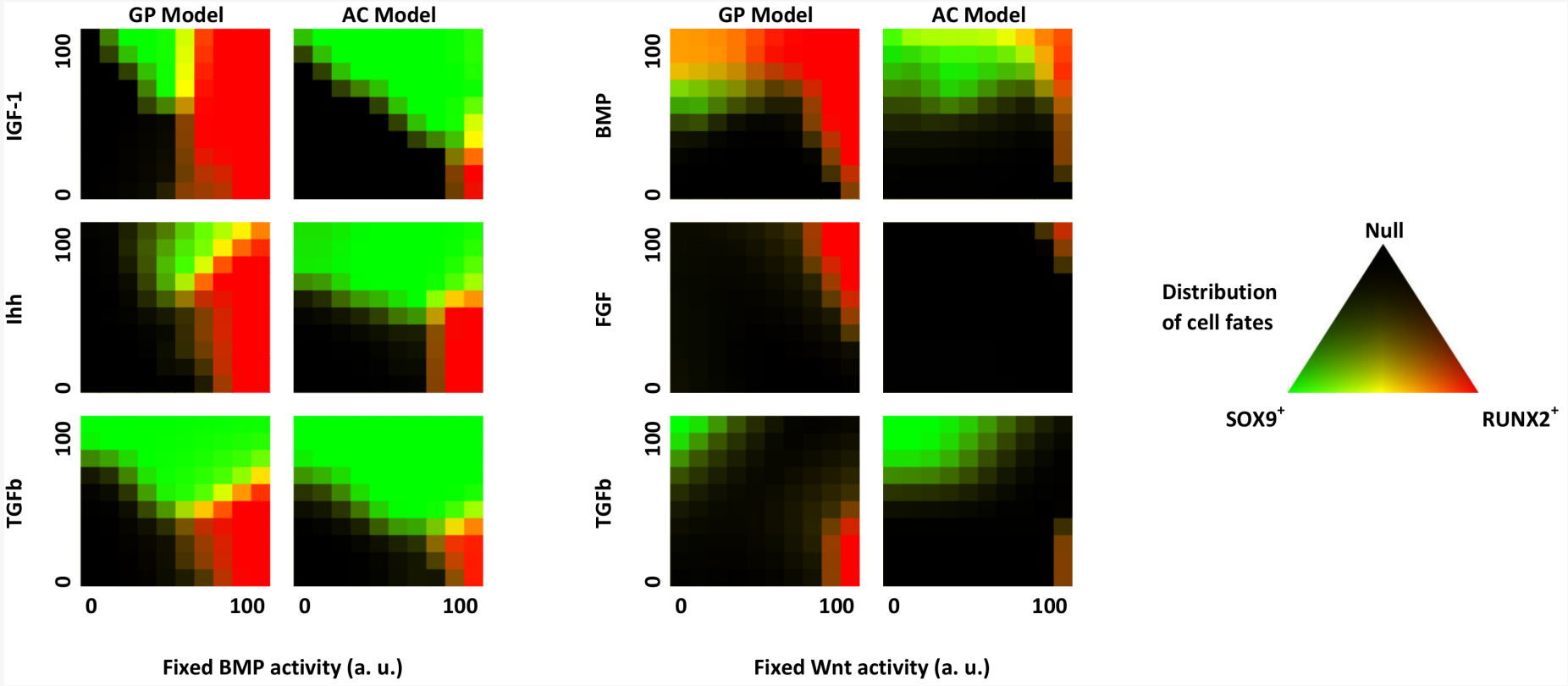
https://doi.org/10.1016/j.cellsig.2019.109471



# ECHO: biologist view


Schivo et al. (2020). *ECHO, the executable CHOndrocyte: A computational model to study articular chondrocytes in health and disease.*

# ECHO: in silico experiments

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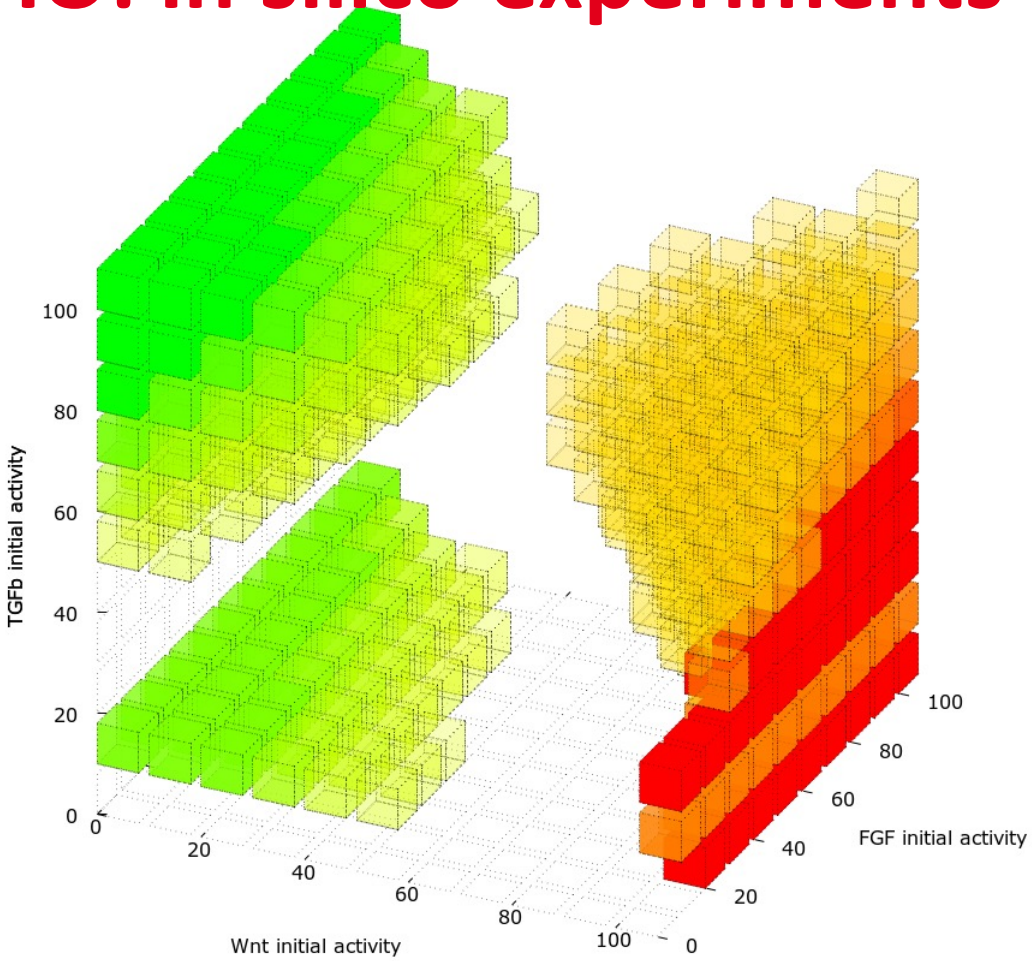
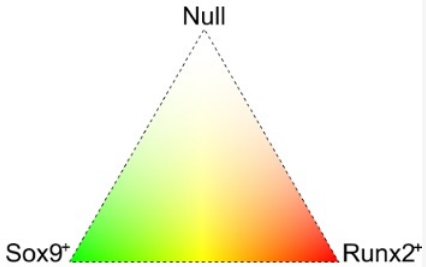
# ECHO: in silico experiments



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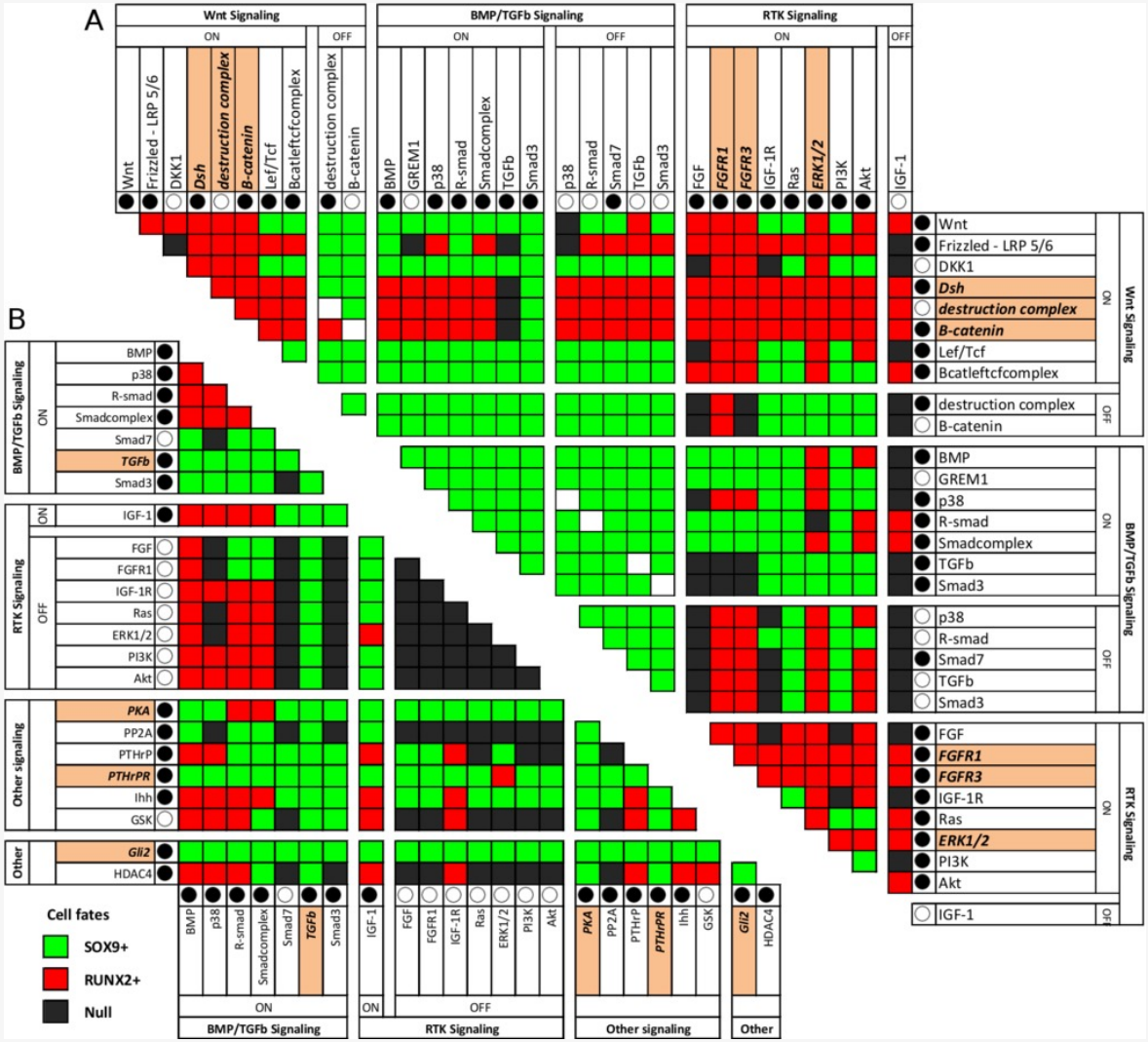
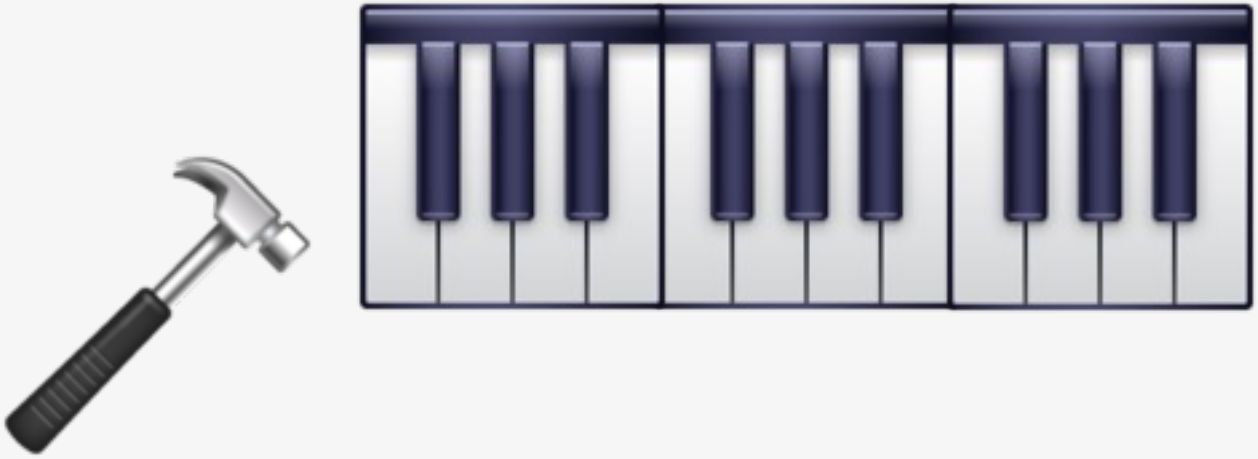



Khurana, Schivo et al. (2021). *An ECHO of cartilage: in silico prediction of combinatorial treatments to switch between transient and permanent cartilage phenotypes with ex vivo validation*

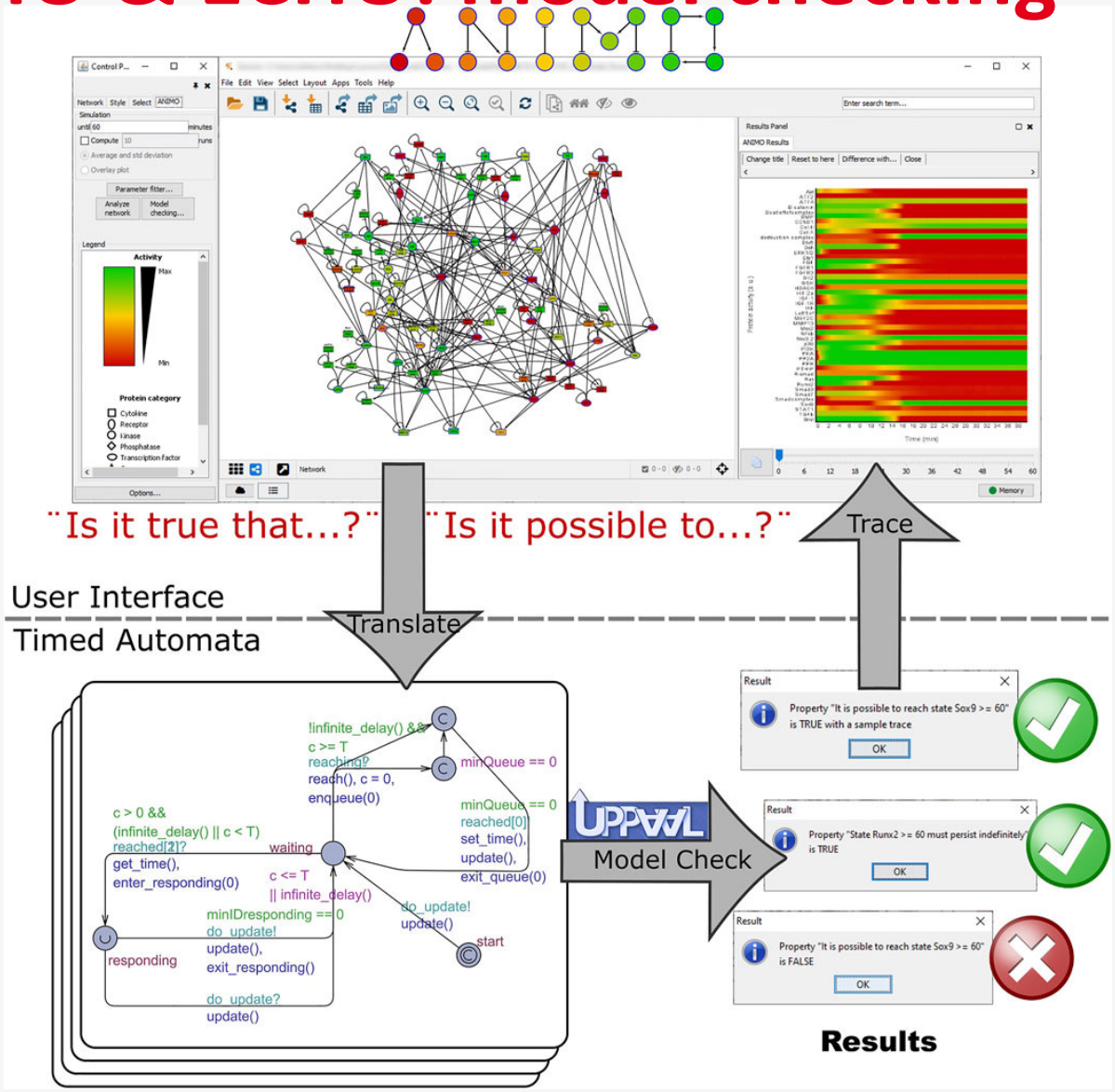
# Model checking ECHO

# Model checking ECHO



# Model checking ECHO

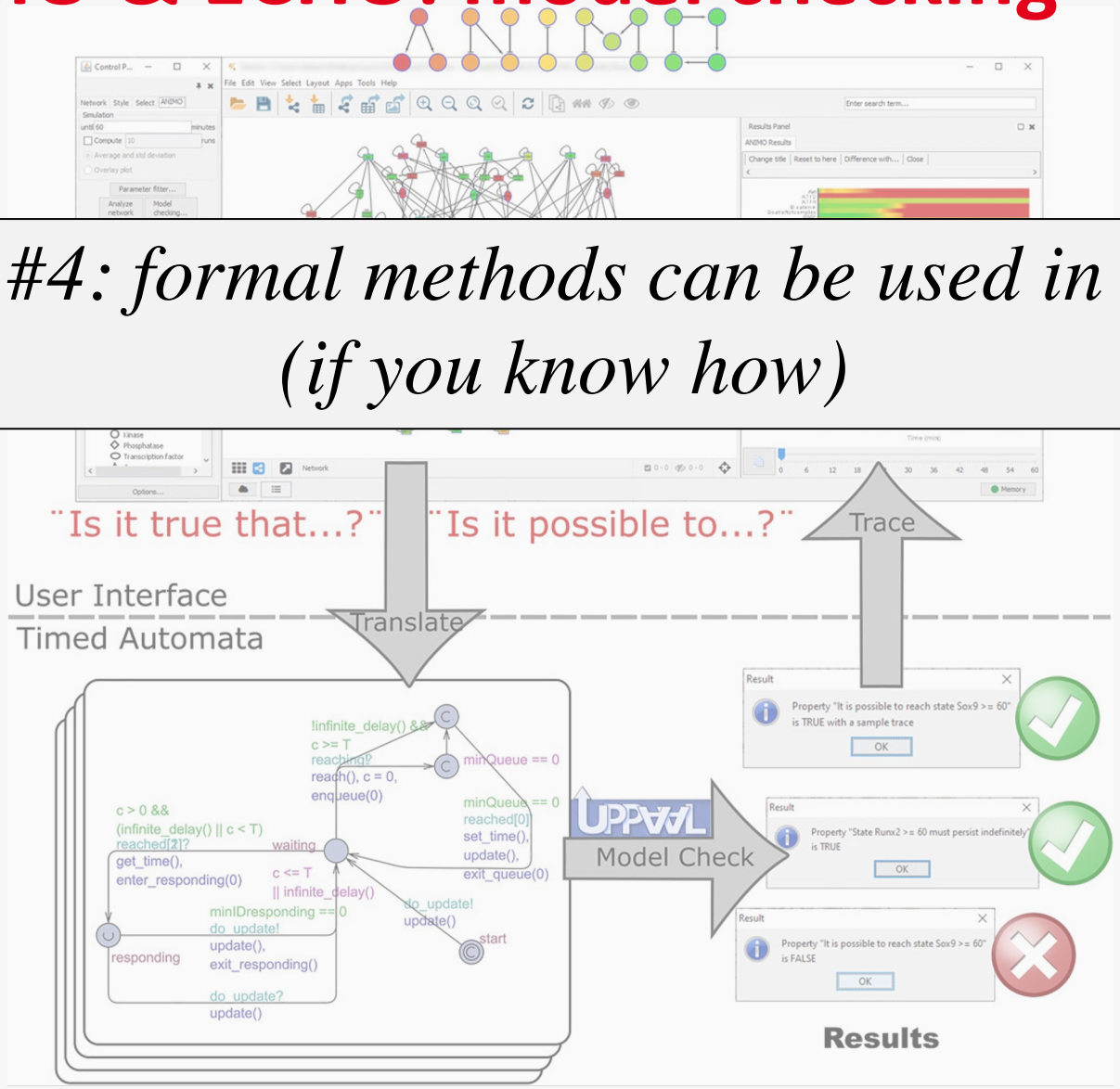
# ANIMO & ECHO: model checking




Khurana, Schivo et al. (2021). *An ECHO of cartilage: in silico prediction of combinatorial treatments to switch between transient and permanent cartilage phenotypes with ex vivo validation*

# ANIMO & ECHO: model checking

*Lesson #4: formal methods can be used in biology (if you know how)*

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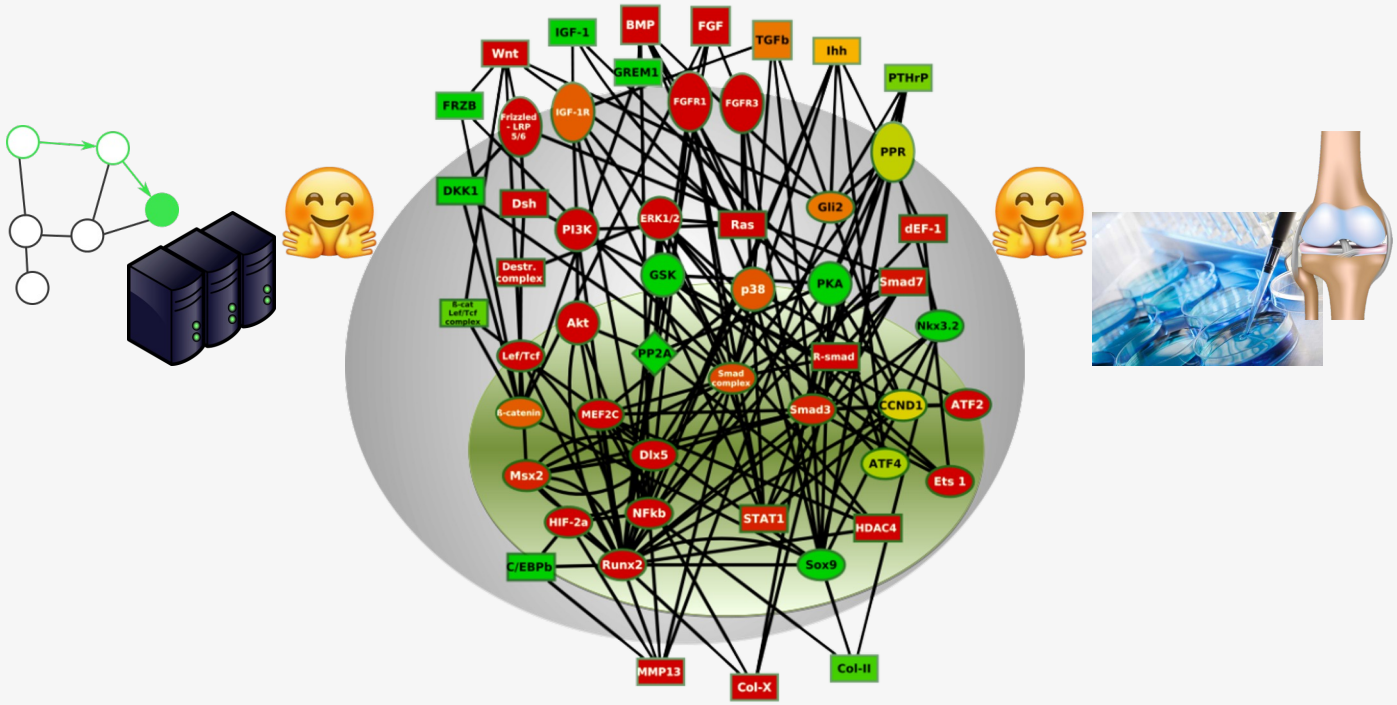
# Back to the end of the story



# Ideas for a happy & fruitful multidisciplinary research

- ✓Lesson #1: listening to the “others”
- ✓Lesson #2: ensure a common terminology
- ✓Lesson #3: start small, go big later
- ✓Lesson #4: powerful models, under the hood

  …?
- ✓Profit!

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