All that glitters is not Deep Learning in Life Sciences (but sometimes it is!)

Jakub M. Tomczak

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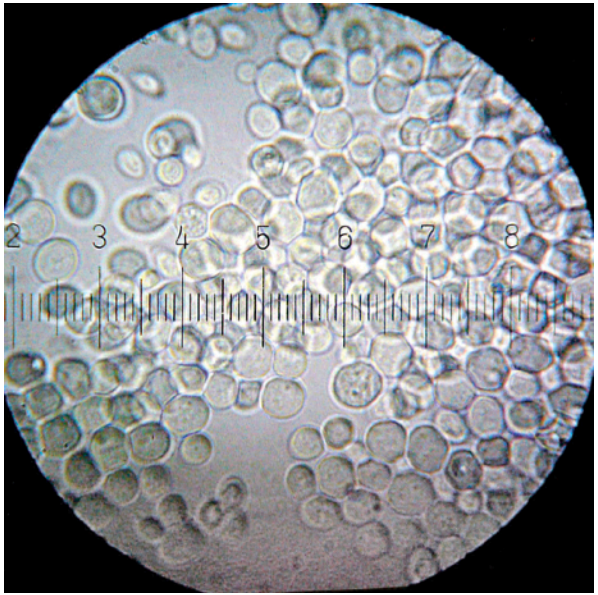
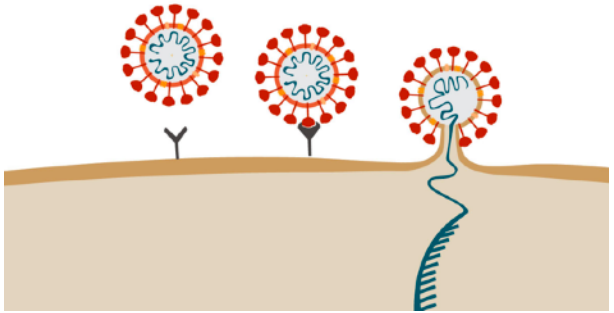
TYPICAL PROBLEMS IN LIFE SCIENCES





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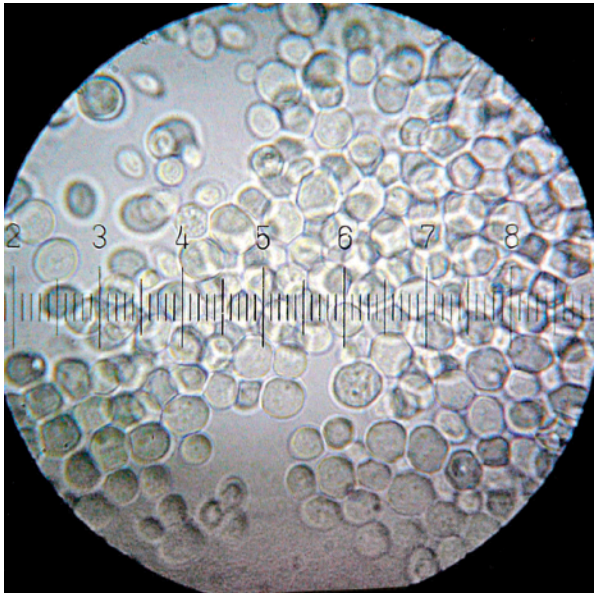
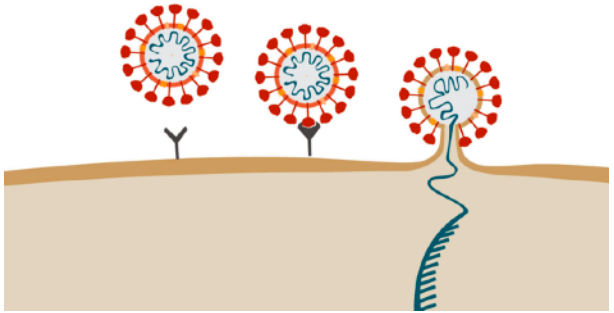


How to model biochemical processes?



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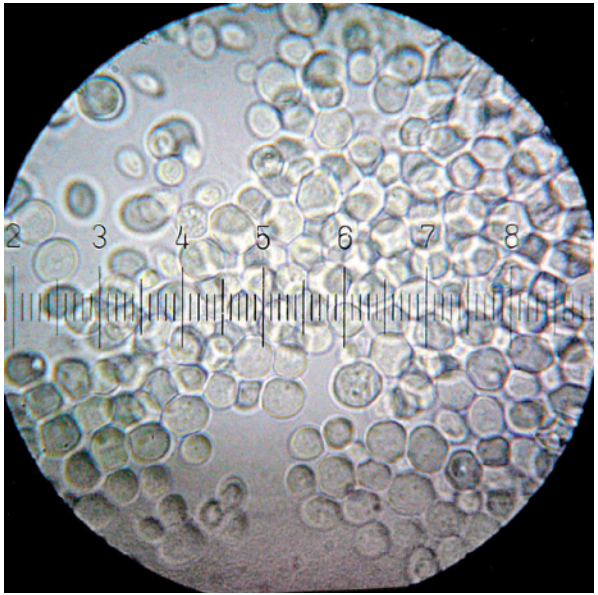
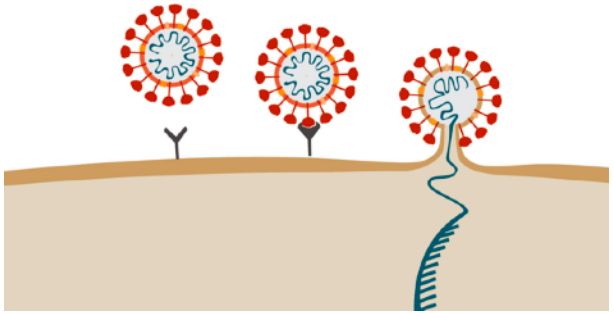


How to model biochemical processes?

How many cells do we see?



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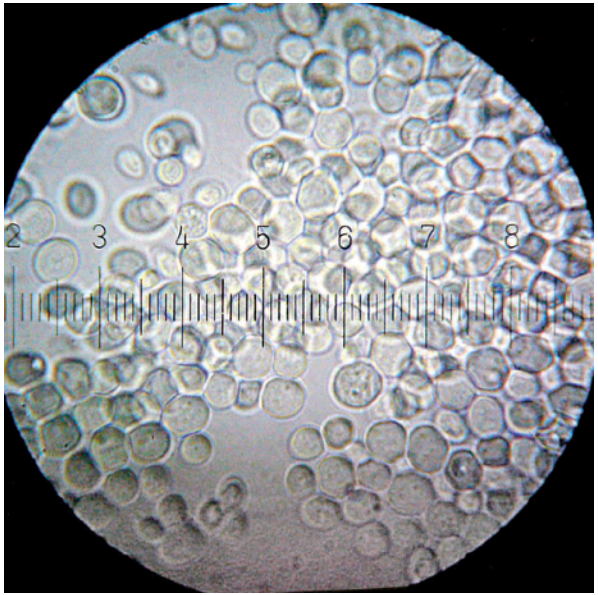

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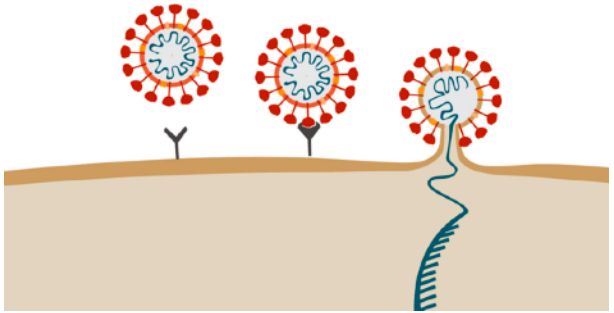
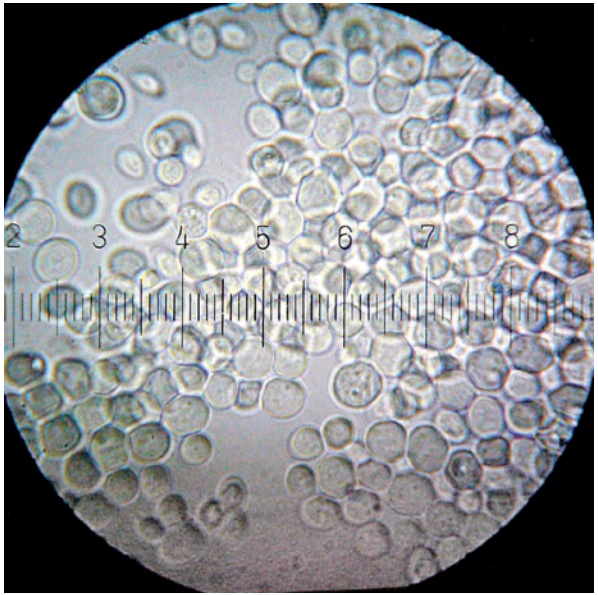


How fast are enzymes catalyzed?

TYPICAL PROBLEMS IN LIFE SCIENCES



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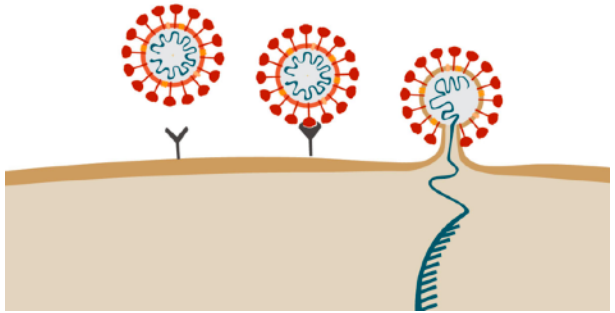
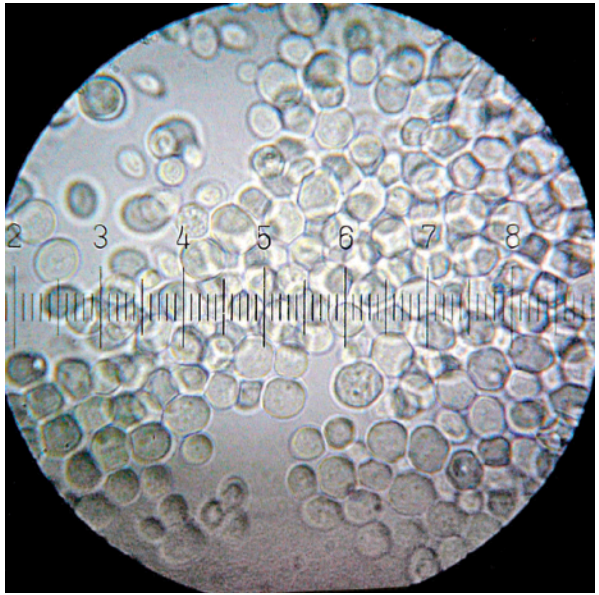


How fast are enzymes catalyzed?

Metabolism

Enzyme kinetics

TYPICAL PROBLEMS IN LIFE SCIENCES



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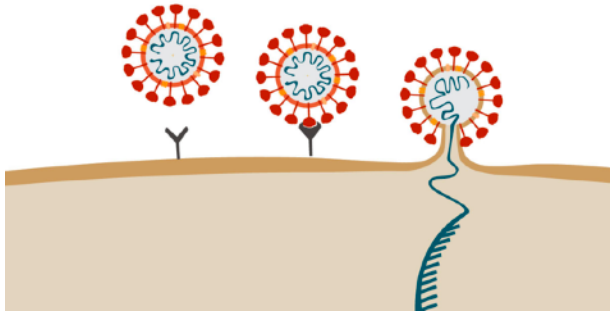


How many cells do we see?

How fast are enzymes catalyzed?

Biochemistry

Anatomy

Physiology

Ecology

Virology

Enzyme kinetics

Metabolism

Cell biology

Microbiology

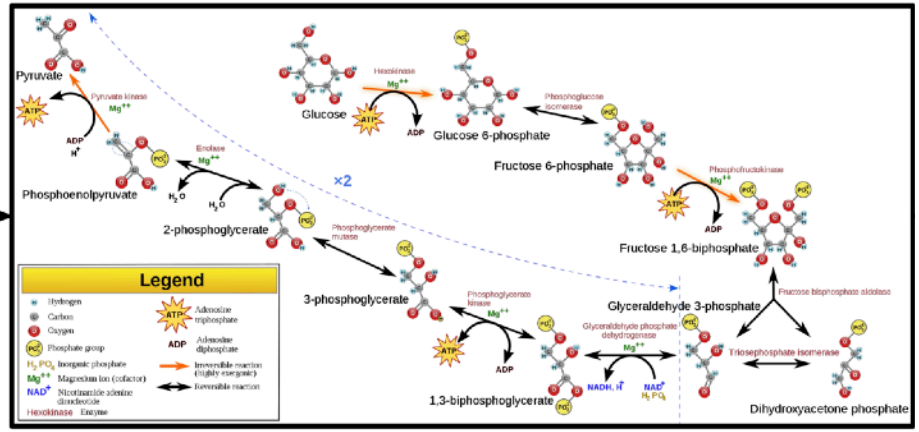
Botany

…

EXAMPLE: GLYCOLYSIS

Input
(nutrients)

EXAMPLE: GLYCOLYSIS



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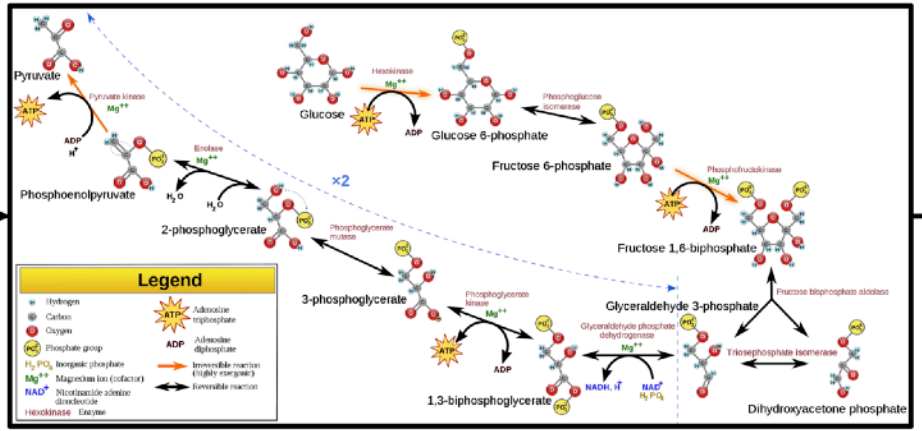
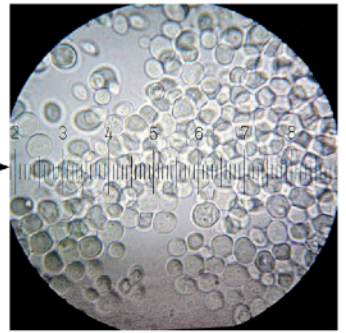
Biochemical processes
(enzymes + products)

EXAMPLE: GLYCOLYSIS





Input
(nutrients)

Biochemical processes
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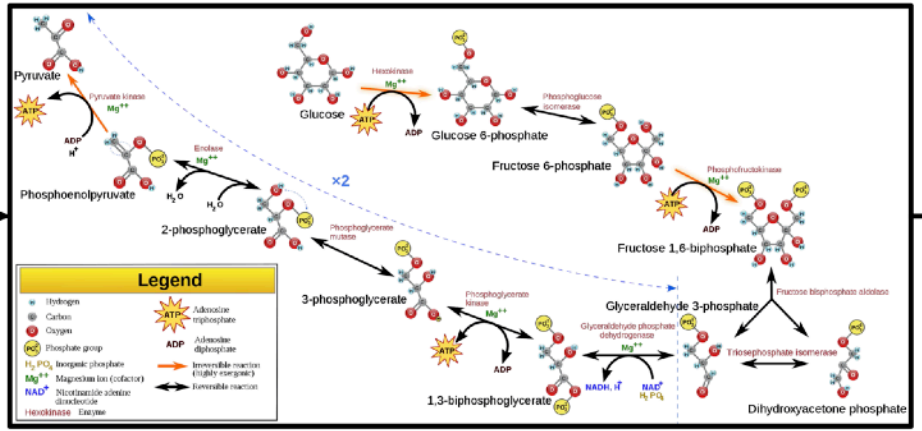
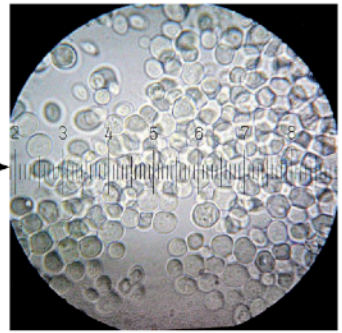
Output
(living cells)

EXAMPLE: GLYCOLYSIS

How to understand the phenomenon?





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Biochemical processes
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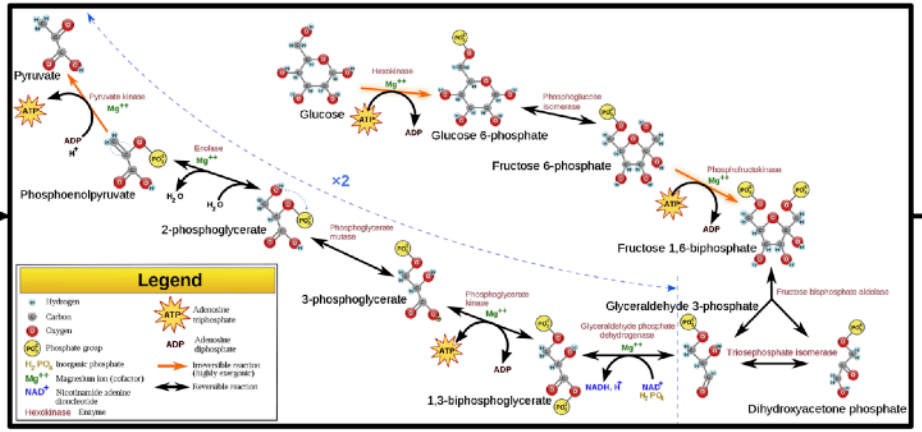
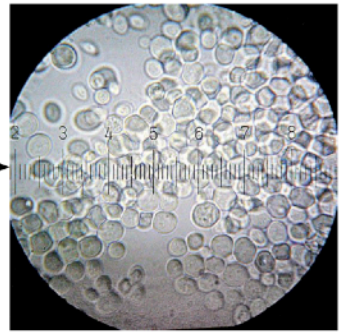
EXAMPLE: GLYCOLYSIS

How to understand the phenomenon?

Model and identify each reaction





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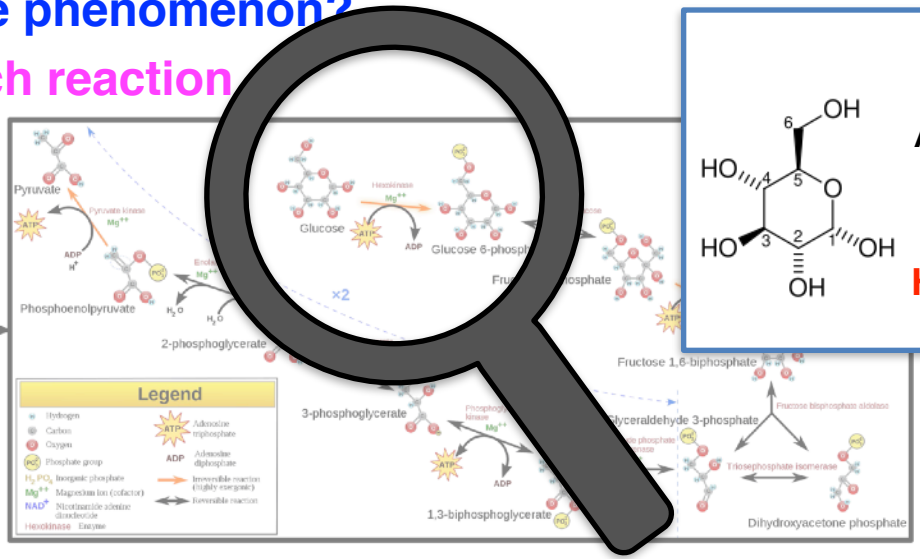

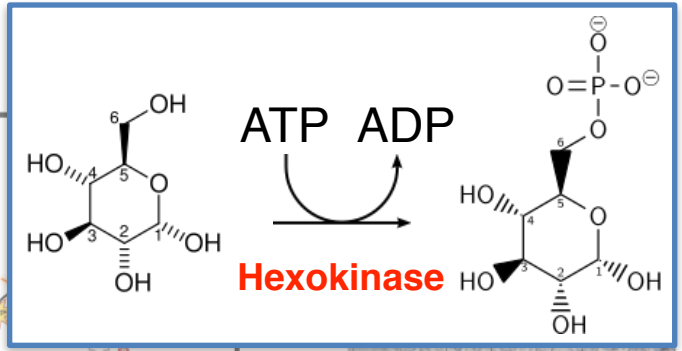

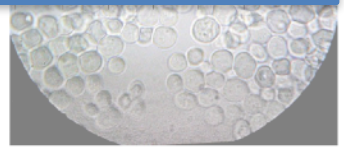

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Biochemical processes
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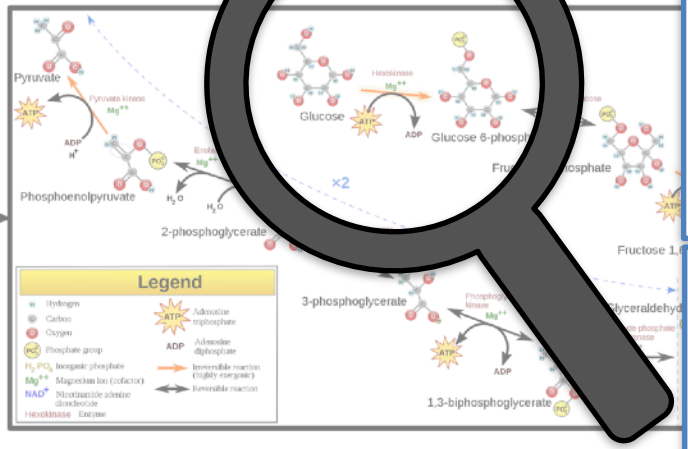
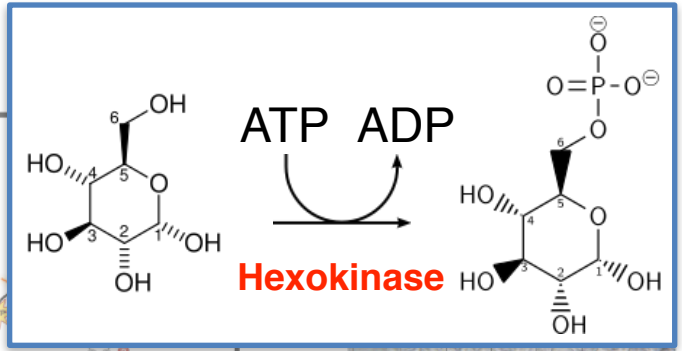




$$v = \frac{E_0 k_{cat} S}{K_M + S}$$

Input (nutrients)

Biochemical processes (enzymes + products)

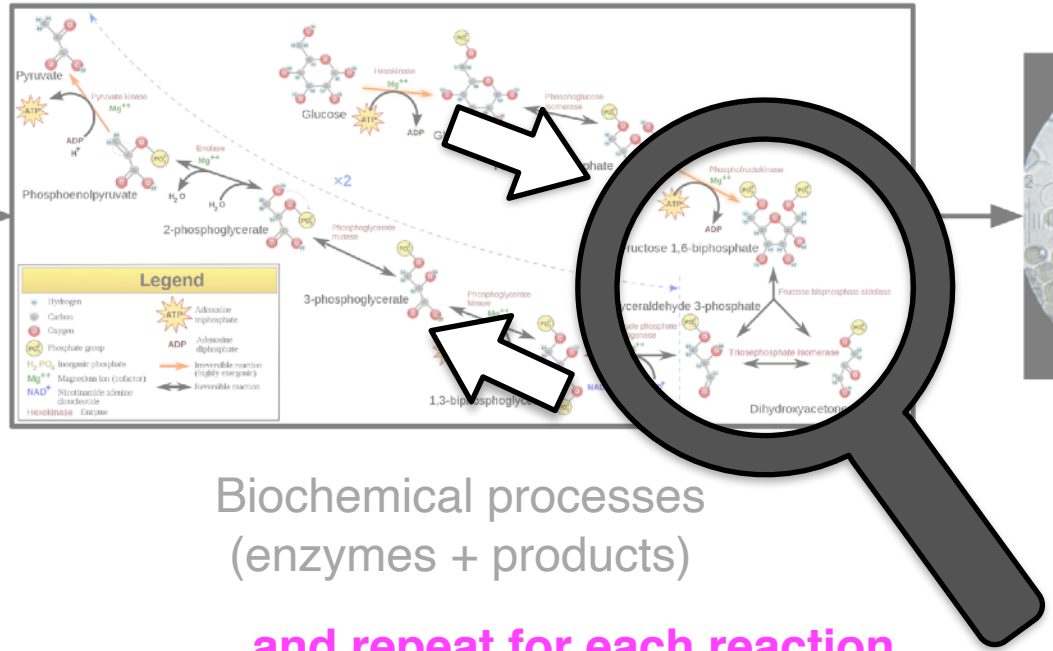
Output (living cells)

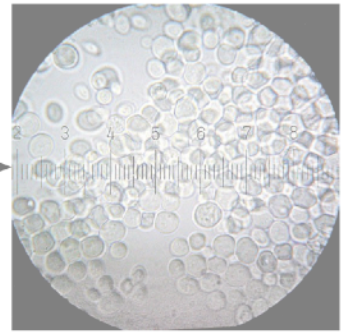
+ DATA (measurements)

EXAMPLE: GLYCOLYSIS

How to understand the phenomenon?

Model and identify each reaction





Input
(nutrients)

Biochemical processes
(enzymes + products)

Output
(living cells)

and repeat for each reaction
(we must be EFFICIENT!)

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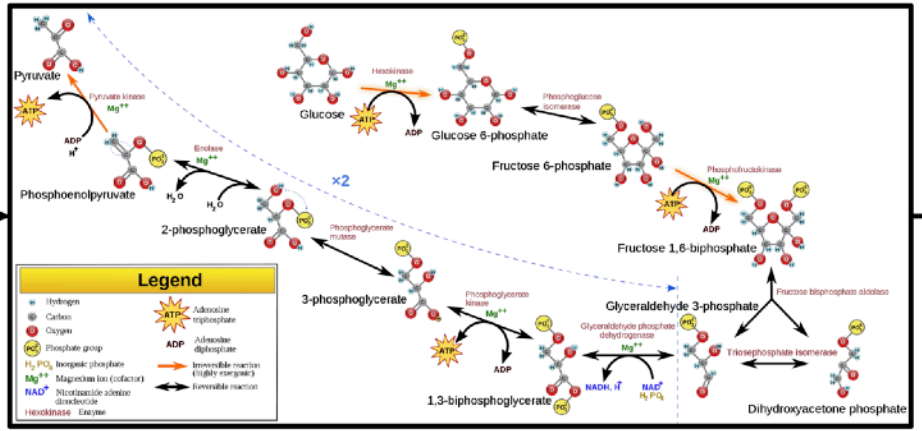
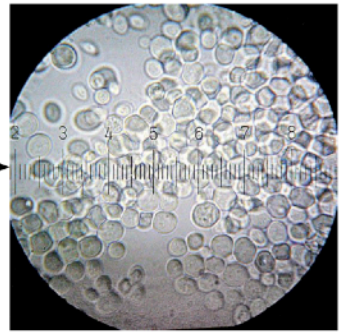
How to understand the phenomenon?





Input
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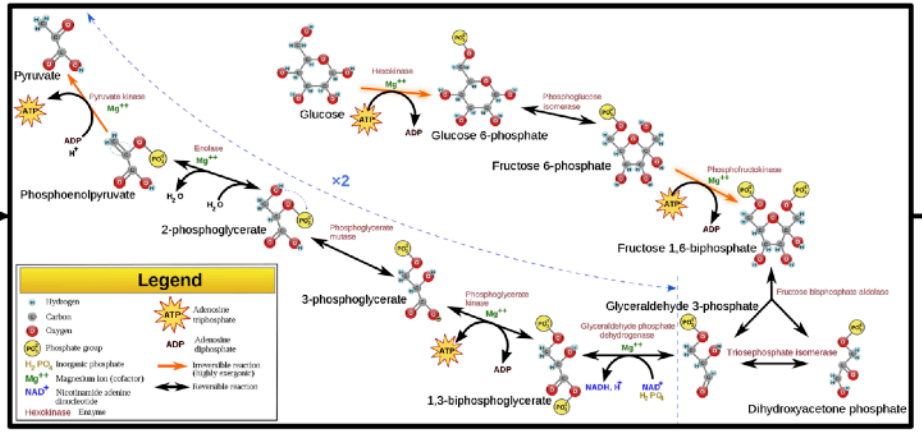
Biochemical processes
(enzymes + products)

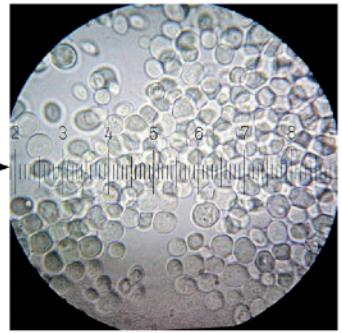
Output
(living cells)

EXAMPLE: GLYCOLYSIS

How to understand the phenomenon?

Model and identify the whole network at once





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Biochemical processes
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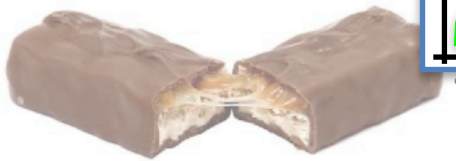

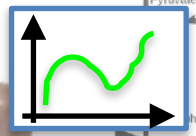

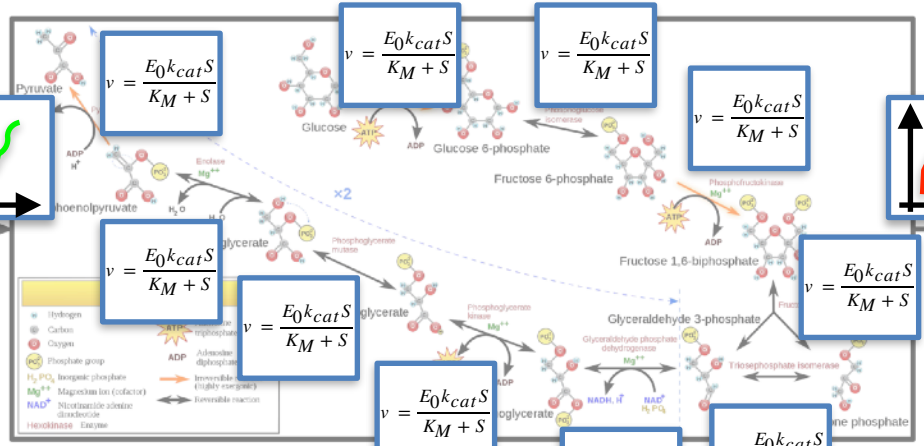

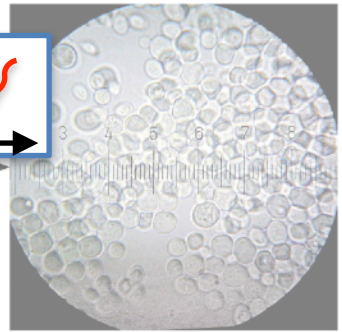

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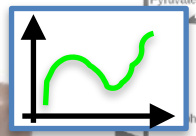

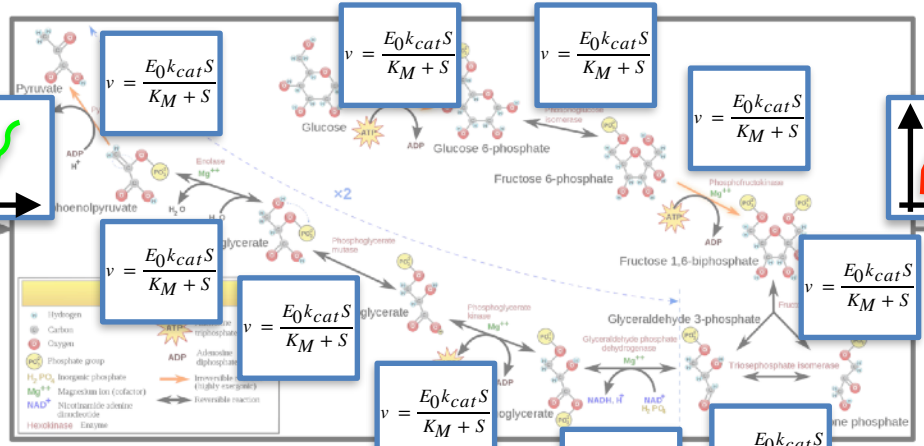

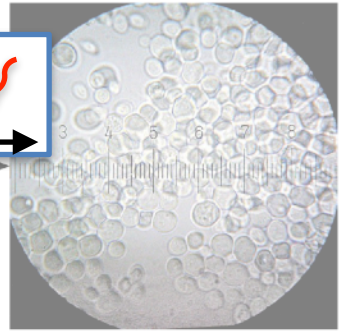

Input (nutrients)

Biochemical pro s (enzymes + products)

Output (living cells)

We know the mathematical description and want to identify the parameters of the network with limited measurements.

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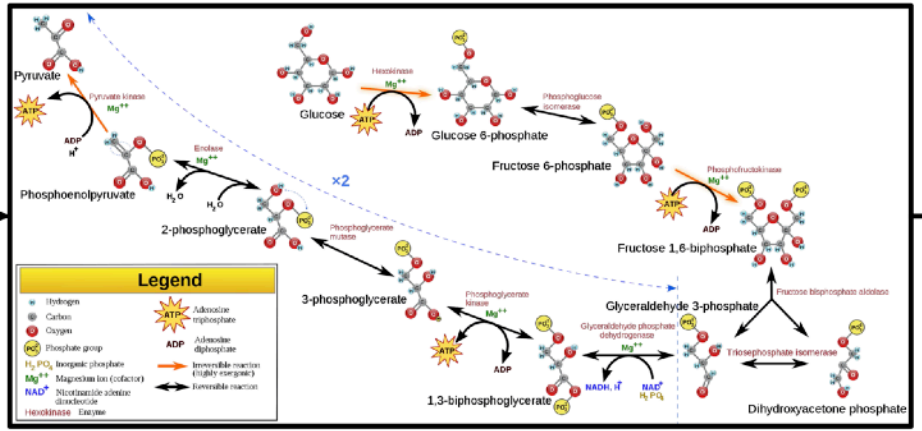

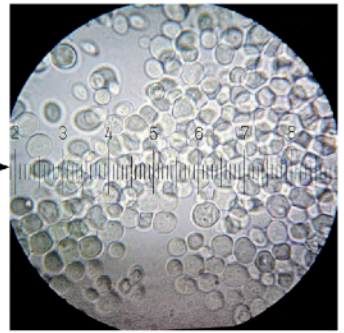

Input
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Biochemical processes
(enzymes + products)

Output
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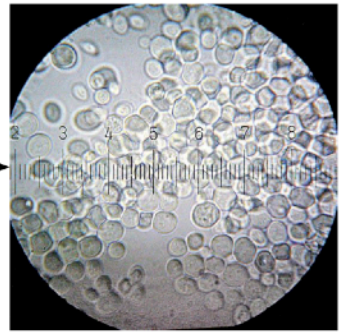
EXAMPLE: GLYCOLYSIS

How to understand the phenomenon?

We don't know the "inside" and treat is as a black-box.



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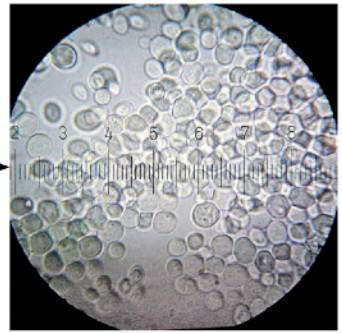

Input
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Biochemical processes
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By learning the input-output dependency, we can understand (to some degree) the phenomenon or use the model to study it.

ENZYME KINETICS: INTRODUCTION

Enzyme kinetics: how the chemical reactions are catalyzed by enzymes.

Goal: Find the reaction rate (i.e., the speed at which a chemical reaction takes place) of ***a single reaction***.

Why?

- Understanding the catalytic mechanism of an enzyme.
- Understanding the role of an enzyme in a chemical reaction.
- Understanding how an enzyme activity is controlled.
- Understanding how a drug (inhibitor) slows down the reaction.

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

The commonly used model in enzyme kinetics is the **Michaelis-Menten model**.

We consider a reversible reaction where an enzyme (E) binds to a substrate (S) to form a complex (ES) to irreversibly release a product (P) and free the enzyme:

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

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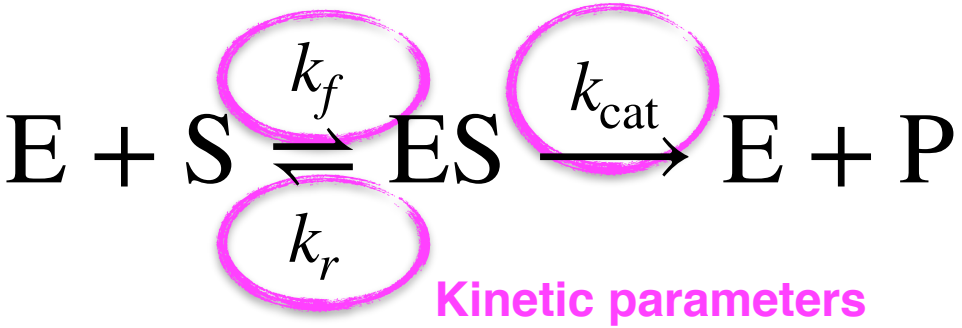

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

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Considering the system in a quasi-steady-state, we get:

$$v = \frac{\mathrm{d}P}{\mathrm{d}t} = \frac{V_{max}S}{K_M + S} = \frac{E_0 k_{cat} S}{K_M + S}$$

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max. velocity

init concentration of enzyme

catalytic rate constant

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Michaelis constant

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$\frac{k_{cat}}{K_M}$ catalytic efficiency

Michaelis constant

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

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Solution:

$$v = V_{max}\left(1 - \exp(-bS)\right)$$

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

How to find the kinetic parameter values? **The standard approach.**

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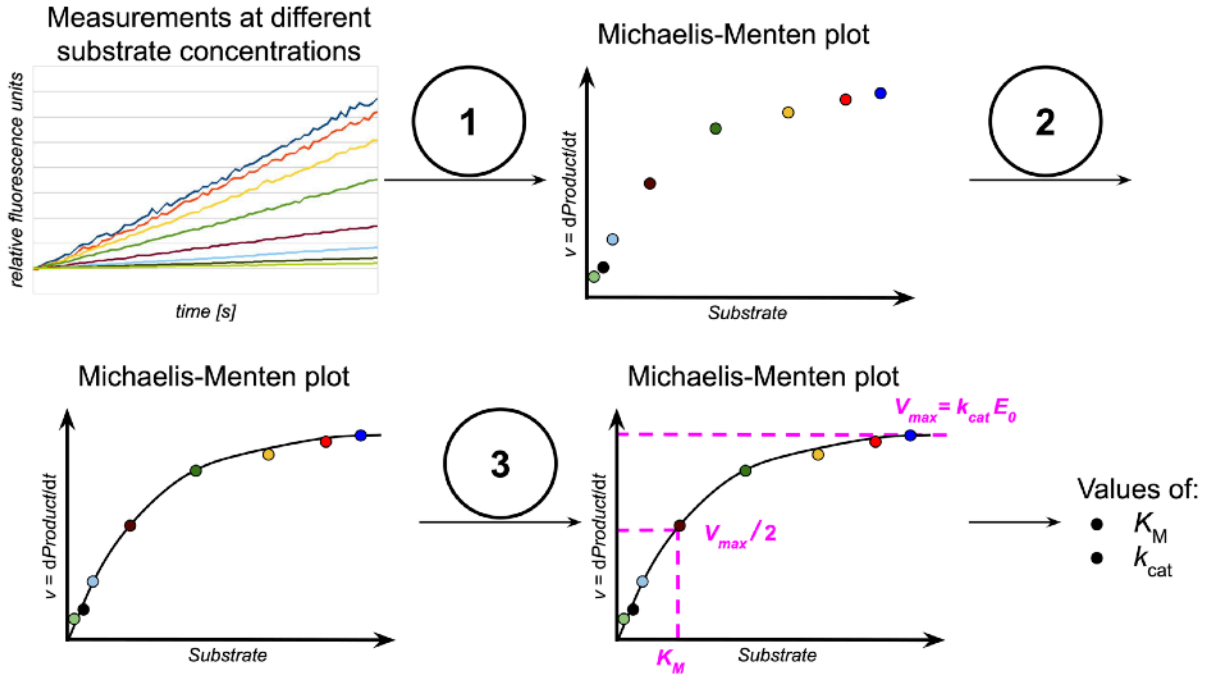

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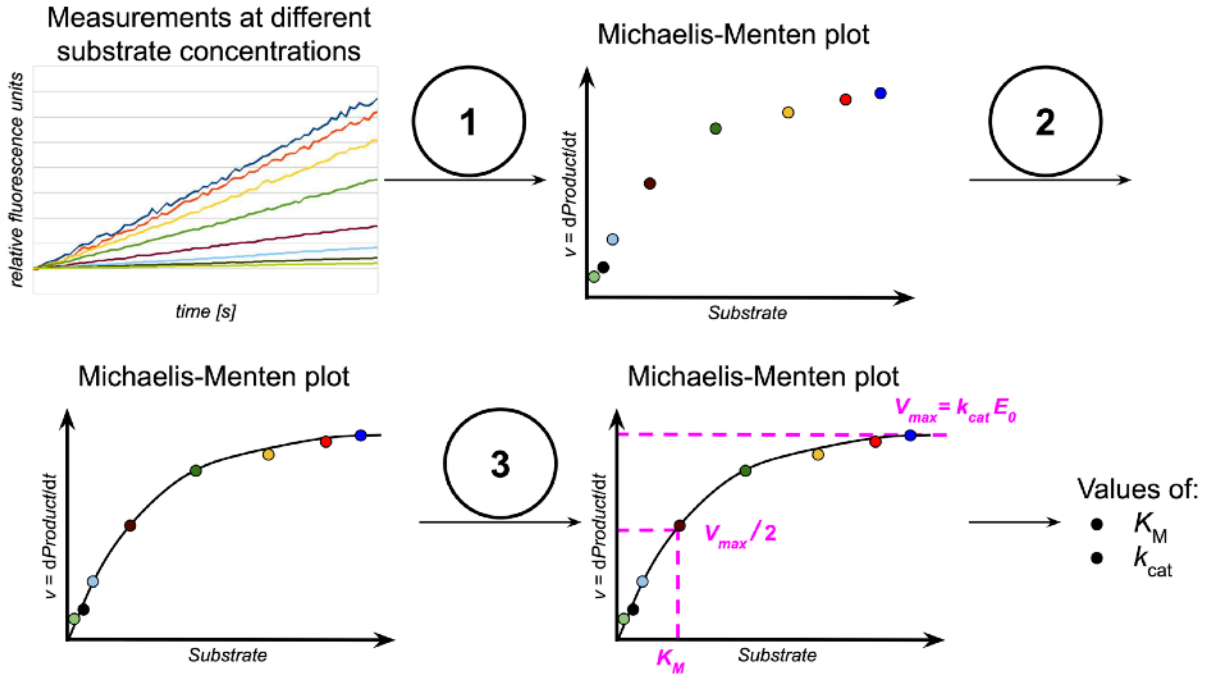

Pros:
- **easy**
- **pretty accurate**

Cons:
- **super laborious**
- **wastes a lot of substrate**
- **time-consuming**

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

How to find the kinetic parameter values? **Our approach: ABC.**

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

How to find the kinetic parameter values? **Our approach: ABC.**

Our main motivation: Use (cheap) computations instead of laborious and costly work in a lab.

Proposition: Use Approximate Bayesian Computation.

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

How to find the kinetic parameter values? **Our approach: ABC.**

1. Initialize $\theta_t := \theta_0$.
2. For $t \in \{0,1,\ldots,T-1\}$:
   (i) (**Generate**) Sample $\theta' \sim q(\theta|\theta_t)$.
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$$\Delta(\theta') = \|x - f(\theta')\|^2$$

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   If $\Delta(\theta') < \varepsilon$, then $\theta_{t+1} := \theta'$.
   Else $\theta_{t+1} := \theta_t$.

ENZYME KINETICS: MICHAELIS-MENTEN MODEL

How to find the kinetic parameter values? **Our approach: ABC.**

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simulator (the MM model)

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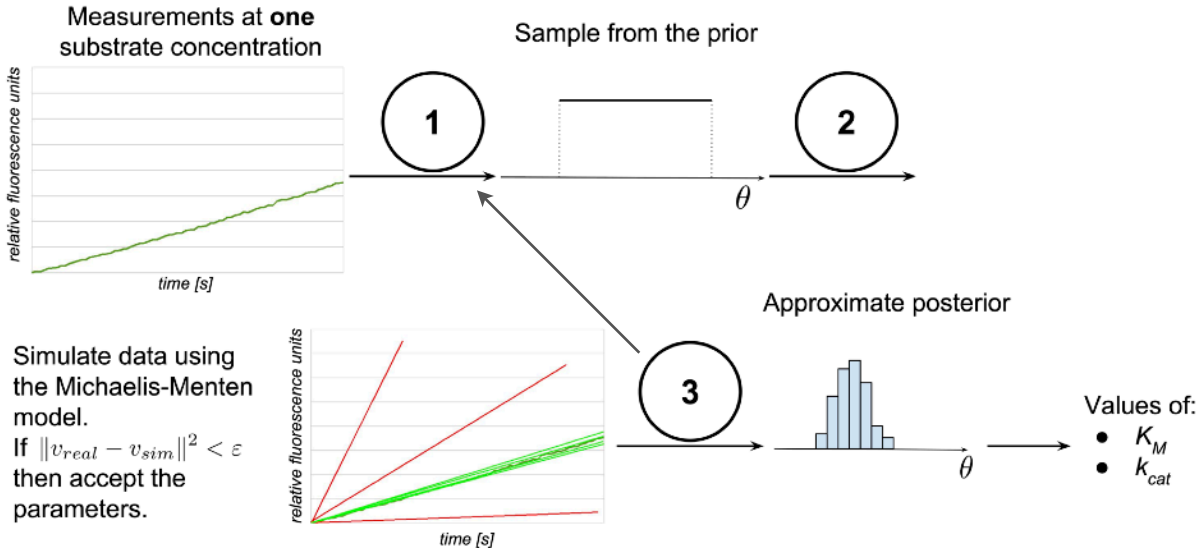

Tomczak, J. M., & Weglarz-Tomczak, E. (2019). **Estimating kinetic constants in the Michaelis–Menten model from one enzymatic assay using Approximate Bayesian Computation**. *FEBS letters*, *593*(19), 2742-2750.

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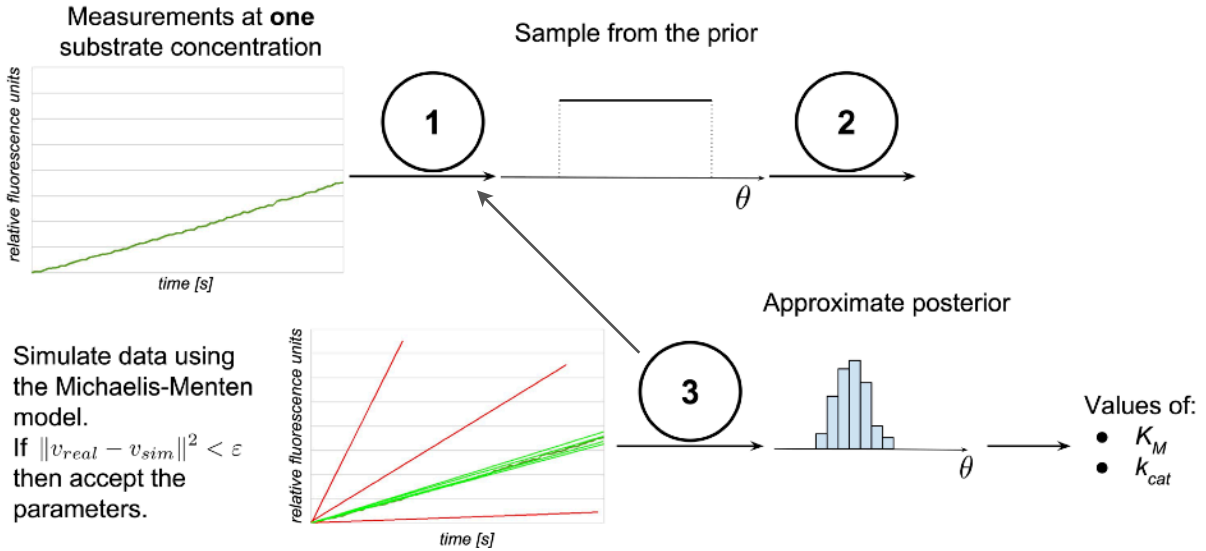

Pros:
- **easy**
- **>10x faster**
- **cheaper!**

Cons:
- **requires prior knowledge**

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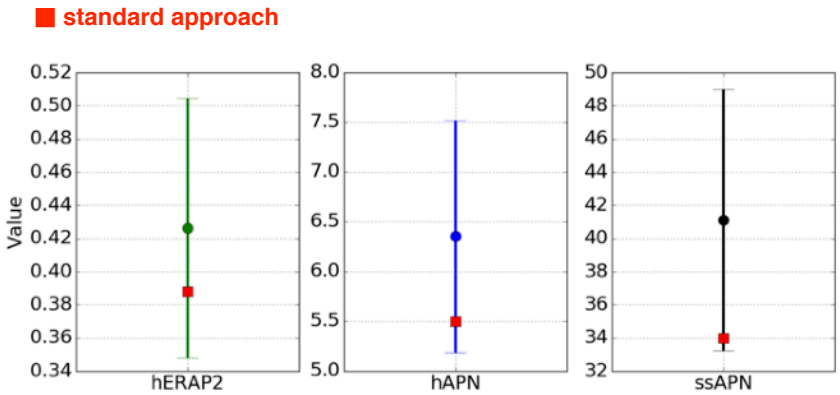
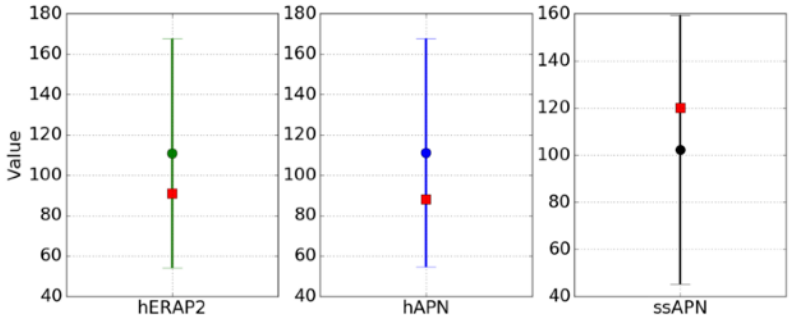
ENZYME KINETICS: THREE AMINOPEPTIDASES

human aminopeptidase (*h*APN), *Sus scrofa* APN (*ss*APN) and human endoplasmic reticulum aminopeptidase 2 (*h*ERAP2)

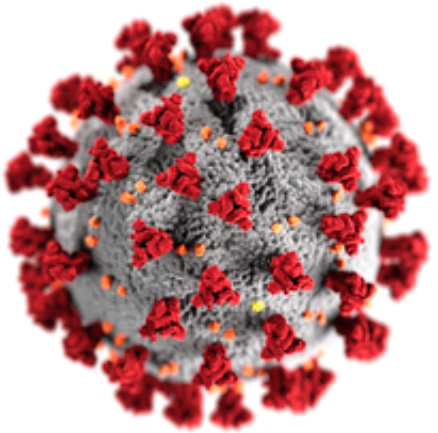


k_{cat}



K_M

ENZYME KINETICS: SARS-COV-1 & SARS-COV-2



In our recent study, we presented:

- An analysis of the active site of PLpro (enzyme) in SARS-CoV-1 (SARS) and SARS-CoV-2 (CoV2).

- A kinetic analysis of the Ub-AMC hydrolysis by PL$_{pro}$ from SARS and CoV2

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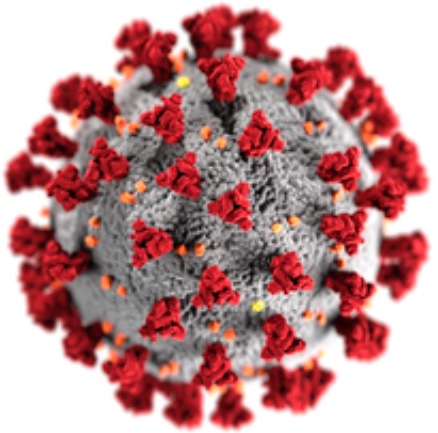

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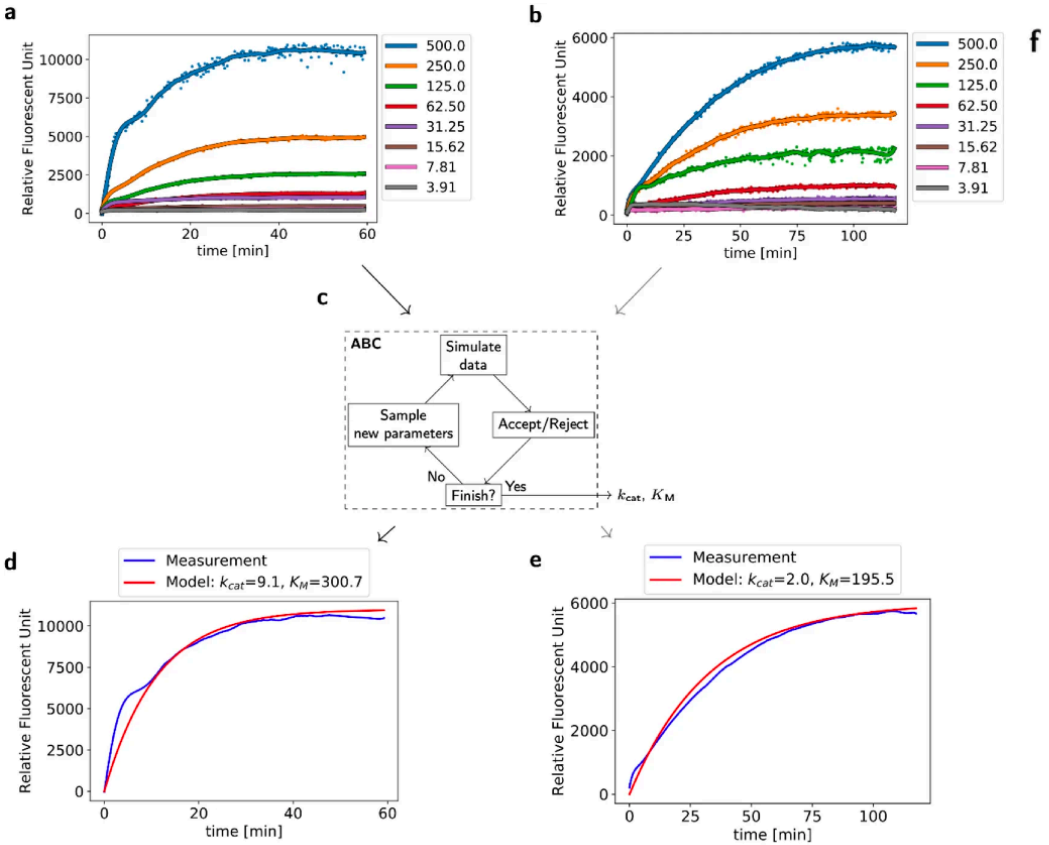

f

	k_{cat} $[s^{-1}]$	K_M $[\mu M]$	k_{cat}/K_M $[s^{-1}M^{-1}]$
PL^{pro}SARS	9.1 ± 0.5	300.7 ± 20.2	**0.030** ± 0.003
PL^{pro}CoV2	2.0 ± 0.3	195.5 ± 5.2	**0.010** ± 0.001

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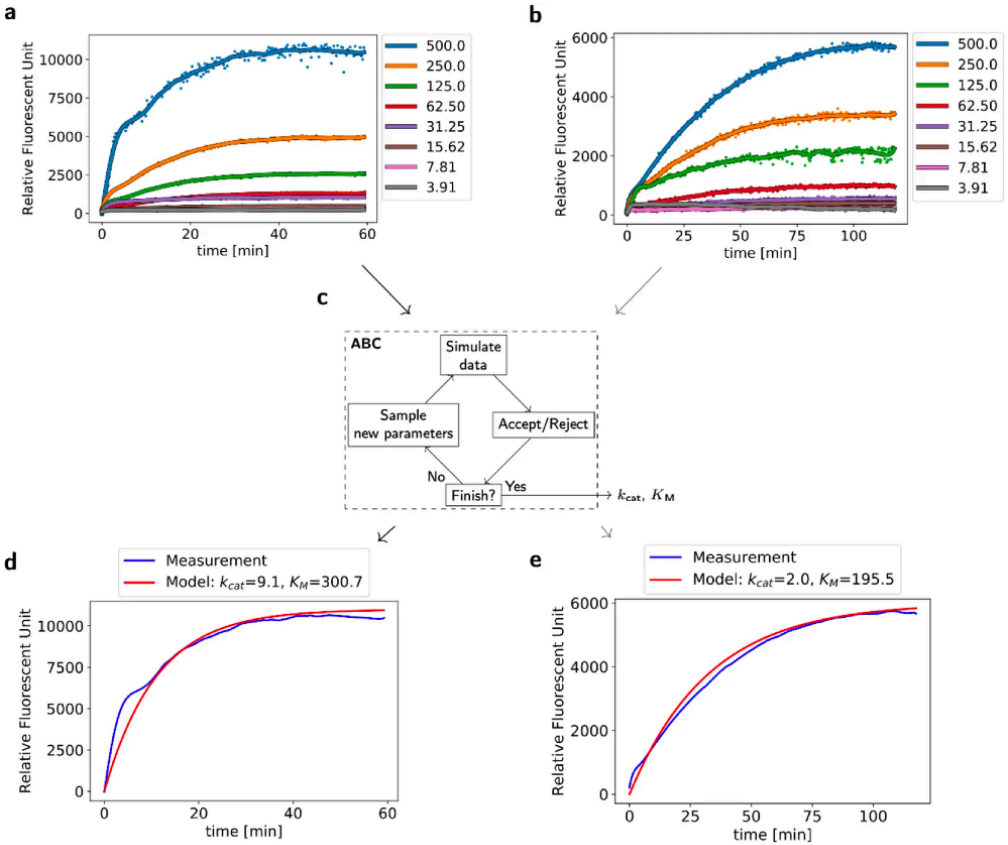

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We see that SARS-CoV-1 is 3 times faster!

This confirms a known fact: once infected, SARS-CoV-1 was overall more aggressive and the disease developed faster.

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IDENTIFICATION OF WHOLE NETWORKS

Let us look at a network of reactions.

IDENTIFICATION OF WHOLE NETWORKS: GENE REPRESSILATOR MODEL

Let us look at a network of reactions.

First, we focus on the well-known gene repressilator model:

$$\frac{dm_1}{dt} = -m_1 + \frac{\alpha}{1+p_3^n} + \alpha_0$$
$$\frac{dp_1}{dt} = -\beta(p_1 - m_1)$$
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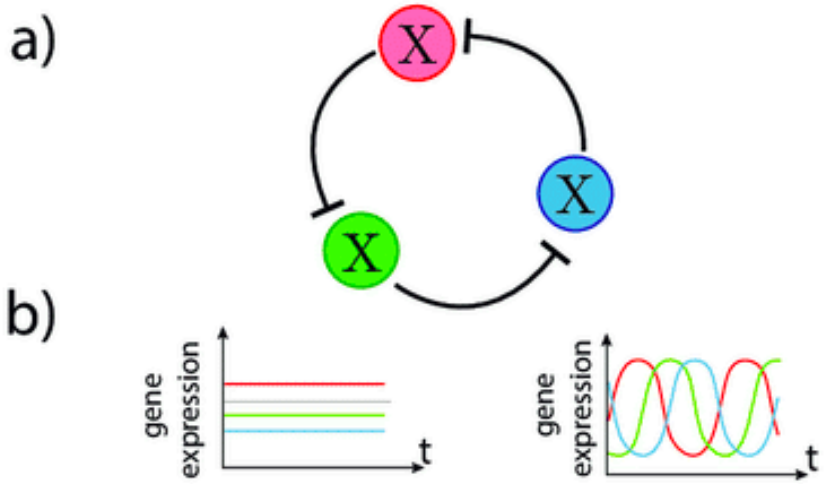

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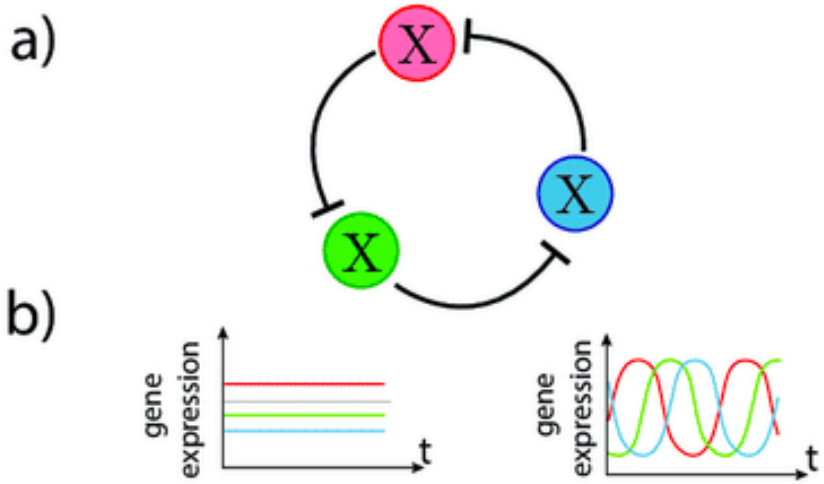

GOAL: Find parameters $[\alpha, \alpha_0, \beta, n]$ by observing only mRNA (m), i.e., gene expression, NOT proteins (p).

IDENTIFICATION OF WHOLE NETWORKS: GENE REPRESSILATOR MODEL

What we know:

- We know the model (i.e., **ODEs**).
- For given parameter values, we can always **run** a numerical integrator.
- There are **four parameters**.

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For instance, we can use **population-based algorithms**.

IDENTIFICATION OF WHOLE NETWORKS: POPULATION-BASED OPT.

- **The key idea**: Run an algorithm multiple times in parallel and exchange information about the objective among solutions.

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- The general scheme:

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2. Repeat until STOP:

   (i) (**Generate**) Generate new solutions, $\mathscr{S}_{t+1}$.

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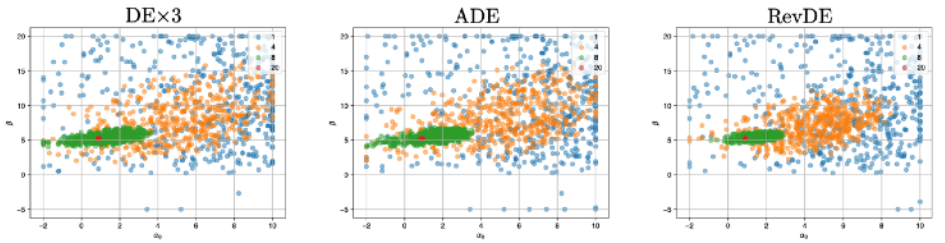
$x_{new} = x_1 + \gamma(x_2 - x_3)$

differential mutation

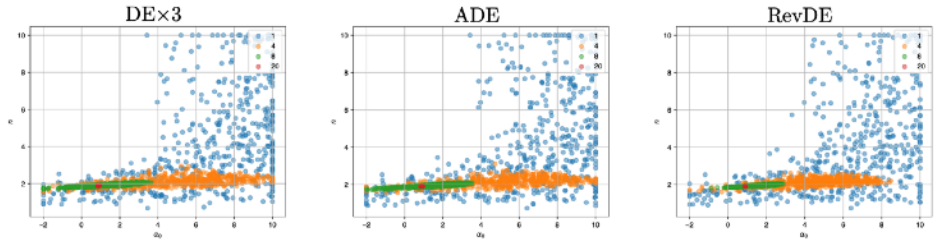
Select best performing candidates from the old population and new points.

VU

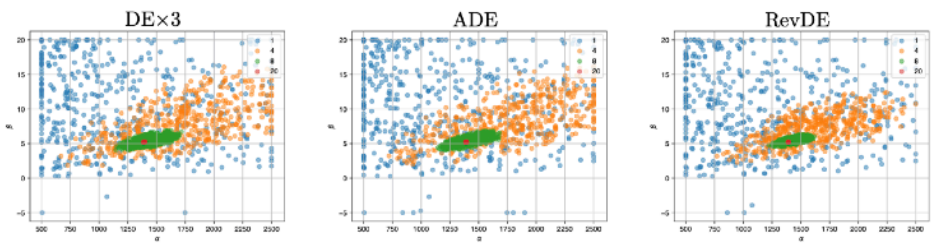
IDENTIFICATION OF WHOLE NETWORKS: GENE REPRESSILATOR MODEL



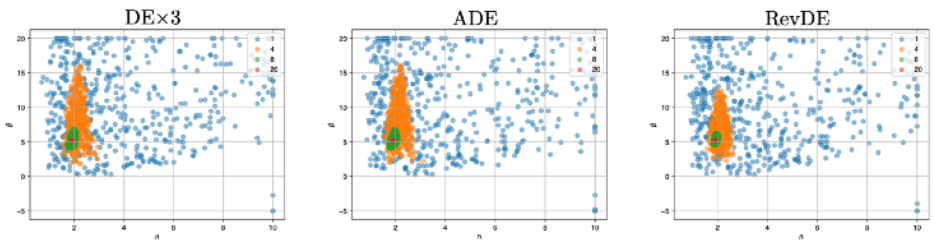
(a) α_0 vs. β



(b) α_0 vs. n



(c) α vs. β



n vs. β

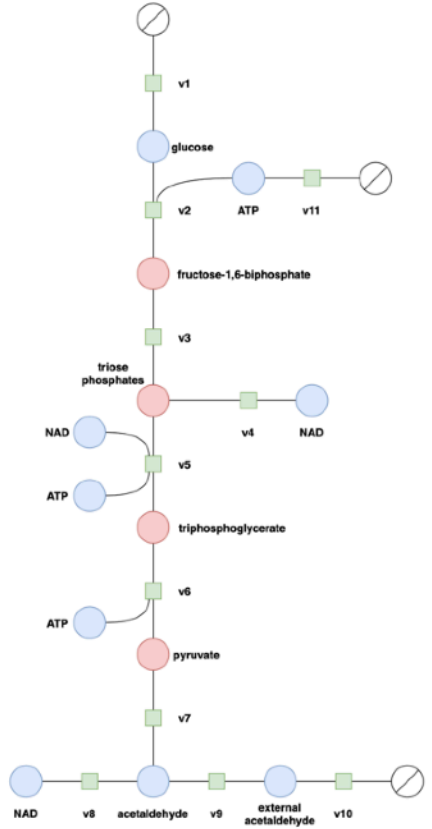
- the 1st generation
- the 4th generation
- the 8th generation
- the 20th generation

Tomczak, J. M., Węglarz-Tomczak, E., Eiben, A. E. (2020). **Differential evolution with reversible linear transformations**. In *Genetic and Evolutionary Computation Conference (GECCO)* (pp. 205-206).

IDENTIFICATION OF WHOLE NETWORKS: GLYCOLYSIS

Now we are ready to attack the larger problem.

We consider the problem **glycolysis** of the baker's yeast.



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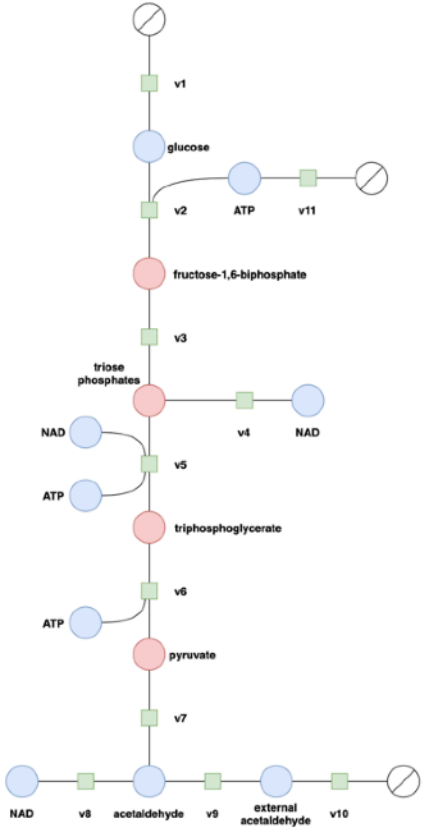
We consider the problem **glycolysis** of the baker's yeast.

The whole glycolysis is extremely complex process.

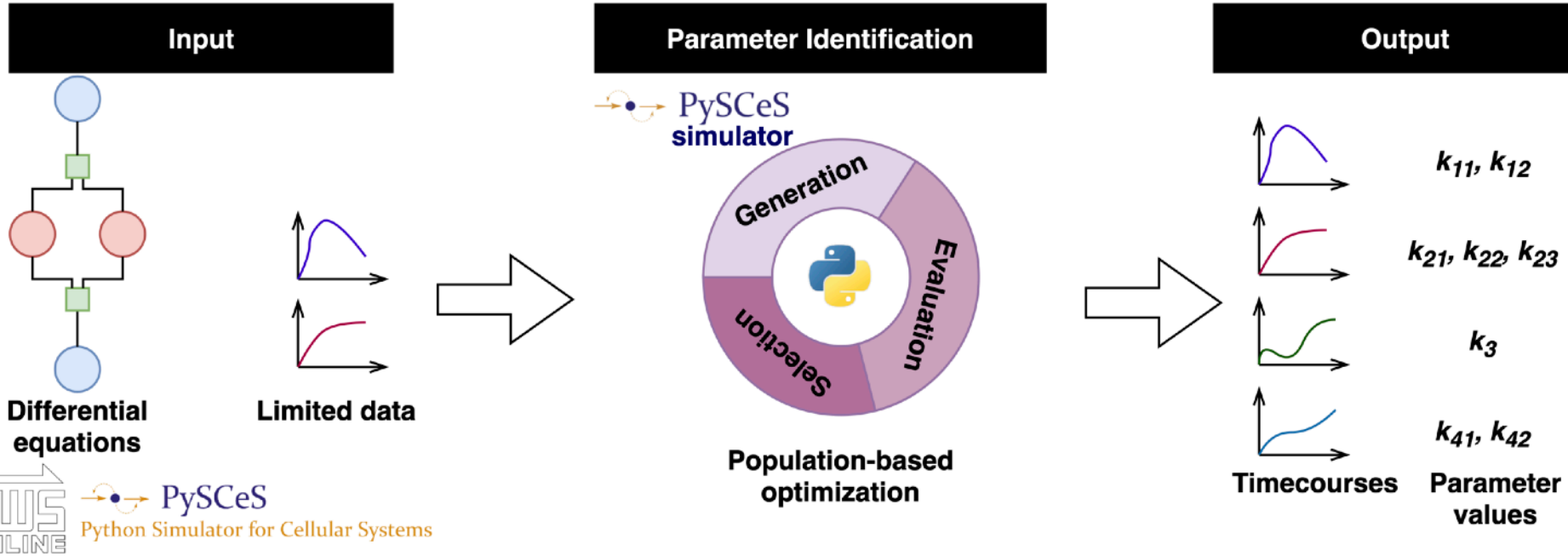
In our studies, we used a simplified model:

- 11 reactions;
- 9 metabolites;
- **18 kinetic parameters**.

We assume that **5 metabolites are observed**.



IDENTIFICATION OF WHOLE NETWORKS: GLYCOLYSIS



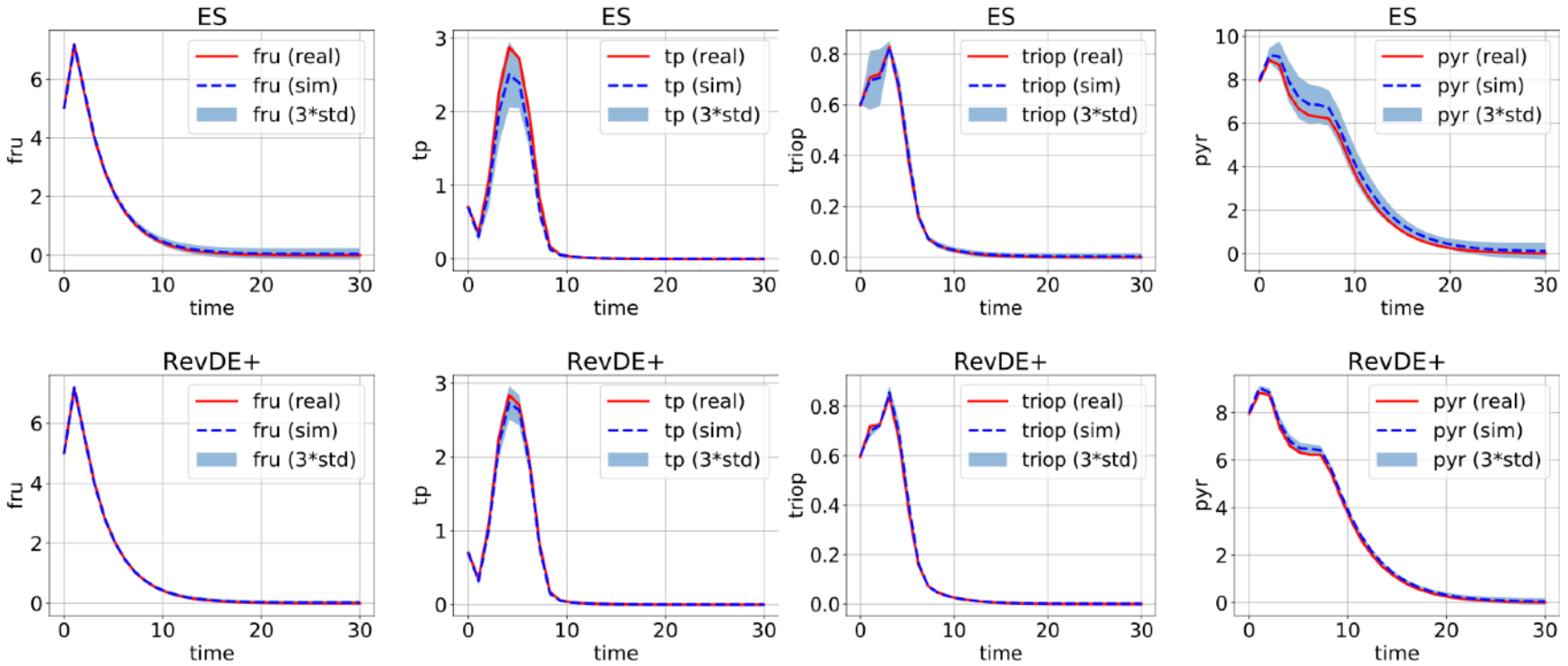
Code: https://github.com/jmtomczak/popi4sb

Weglarz-Tomczak, E., Tomczak, J. M., Eiben, A. E., & Brul, S. (2021). **Population-Based Parameter Identification for Dynamical Models of Biological Networks with an Application to Saccharomyces cerevisiae**. *Processes*, *9*(1), 98.

VU

IDENTIFICATION OF WHOLE NETWORKS: GLYCOLYSIS

Unobserved metabolites



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(AUTOMATIC) CELL COUNTING: THE CASE OF CANCER CELLS

Input
(nutrients)

Black box

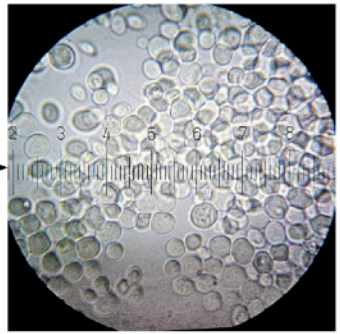

Image +
counts of cells

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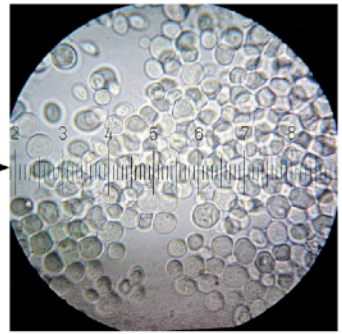

Input
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Image +
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ASSUMPTIONS:

(i) We don't know how the cancer develops.

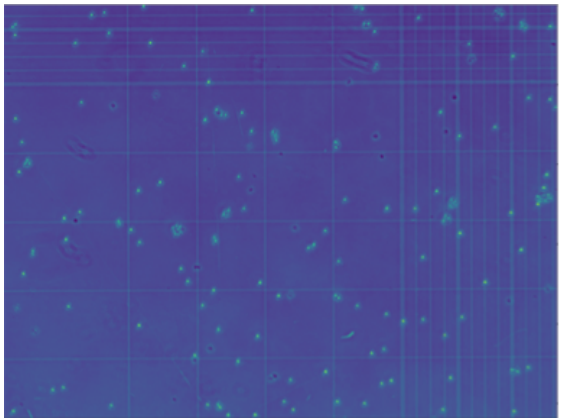
(ii) We give different nutrients to determine how they influences cancer.

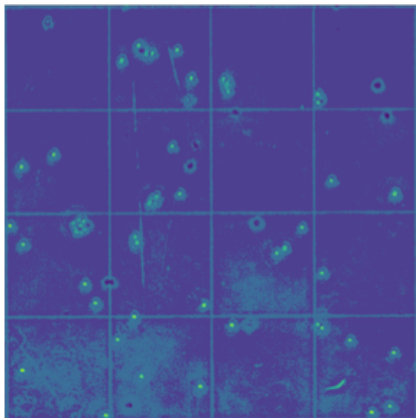
GOAL: Automatically calculate cells and treat is as a regression task.

(AUTOMATIC) CELL COUNTING: THE CASE OF CANCER CELLS

Data:

- a human osteosarcoma (U2OS) and a human leukemia (HL-60)
- 165 images (133 training, 32 test)
- 700px by 700px
- Collected at the UvA (led by E.W.-T.)





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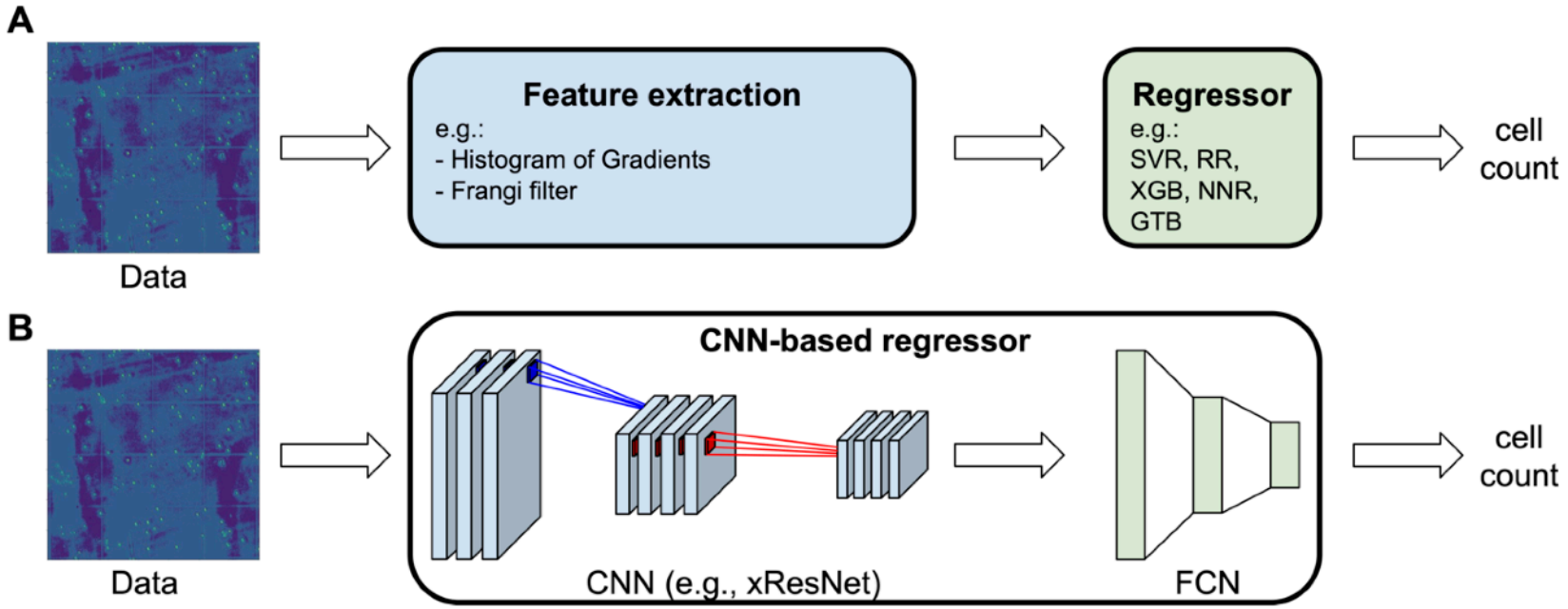

A: Machine learning pipeline. **B:** Deep learning approach.

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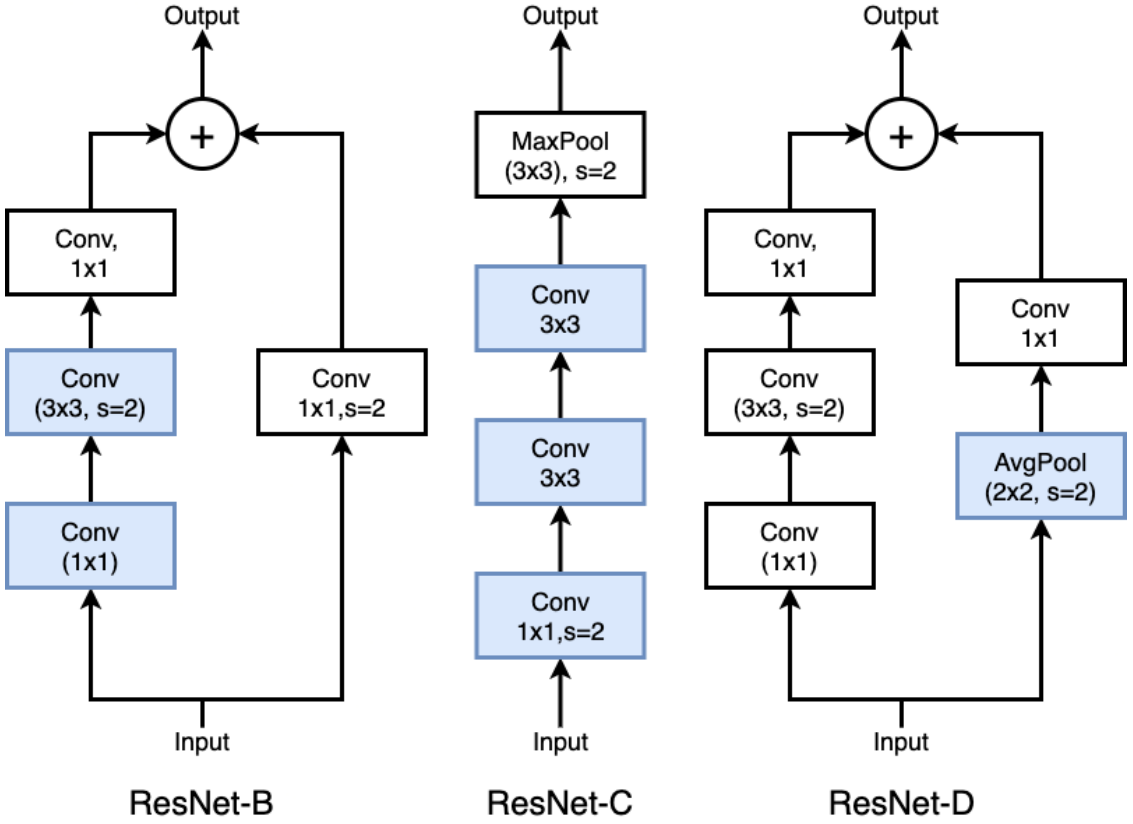
(AUTOMATIC) CELL COUNTING: THE CASE OF CANCER CELLS

We used **xResNet** + **transfer learning**.



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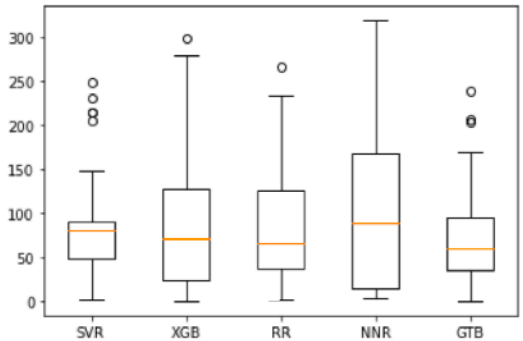
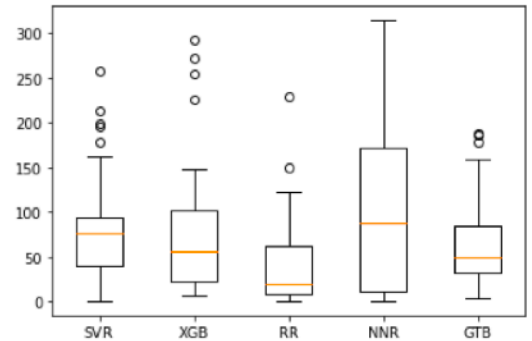
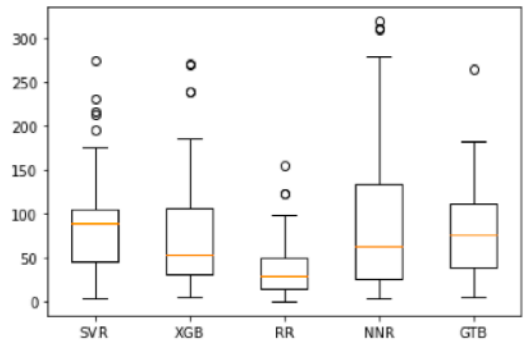


Image



HOG

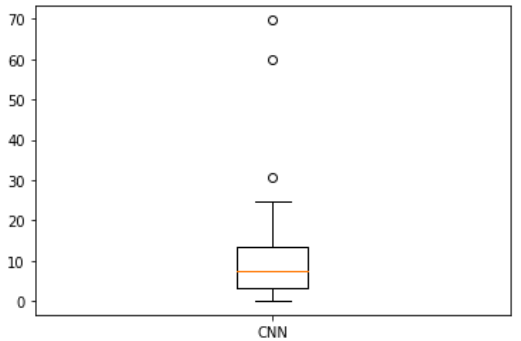


Frangi

Machine learning pipeline: min. avg. error = **40**

CNN w/ TL: avg. error = **33**

CNN w/ TL: avg. error = **12**



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- Computational methods give a great opportunity to study our reality.
- AI-powered tools are useful from nano to macro scale.
- We should always try to use as much of prior knowledge as possible.
- Deep learning is not an answer to all questions.

THANK YOU FOR YOUR ATTENTION

Jakub M. Tomczak
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Vrije Universiteit Amsterdam

Webpage: https://jmtomczak.github.io/

Github: https://github.com/jmtomczak

Twitter: https://twitter.com/jmtomczak