Measuring Periodicity in Gene Expression with Persistence

I. Methods : Stability

II. Motivation : Somitogenesis

III. Methods : Measures

IV. Results : Rankings

I. Methods: Stability

I.1 FUNCTIONS

function

$f : S^1 \to \mathbb{R}$

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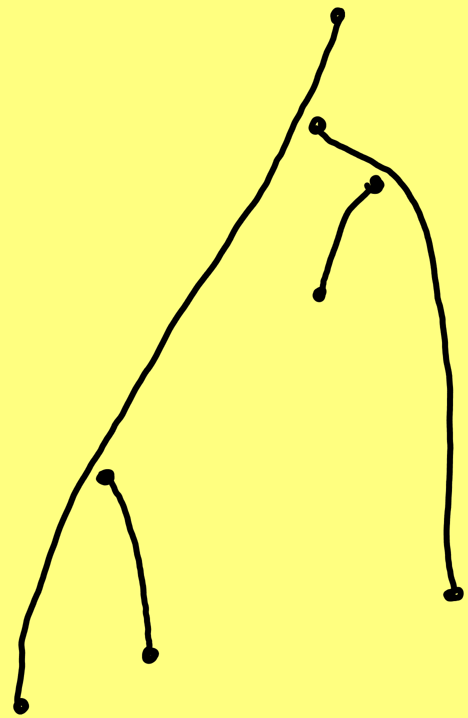

merge tree

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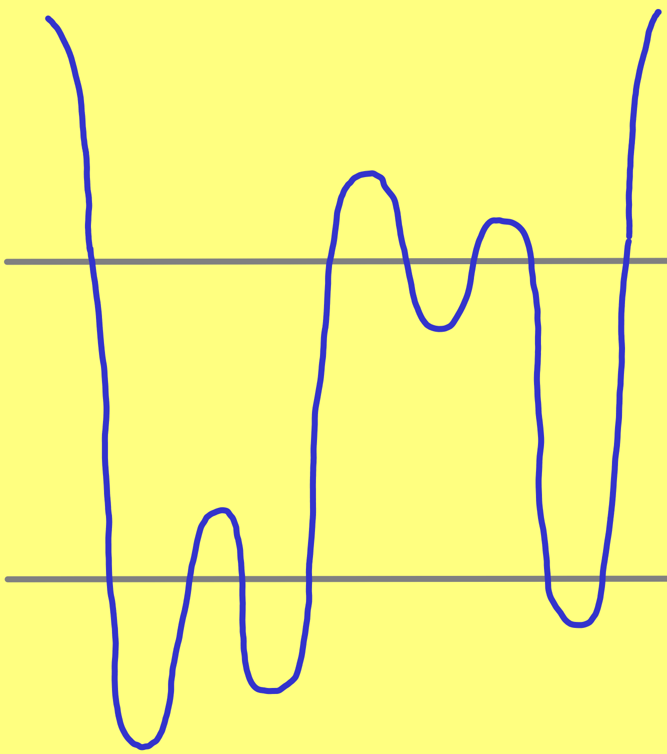

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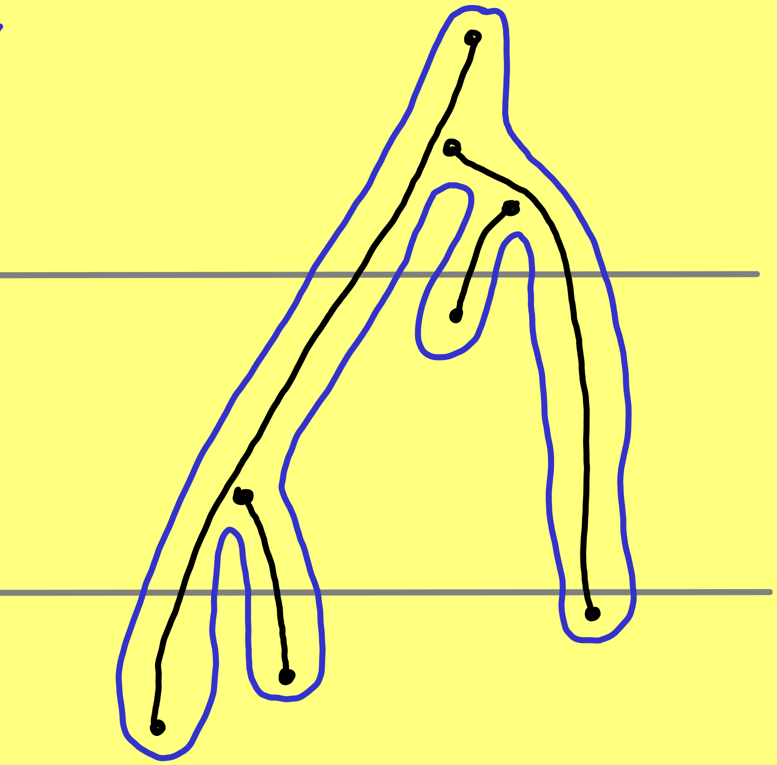

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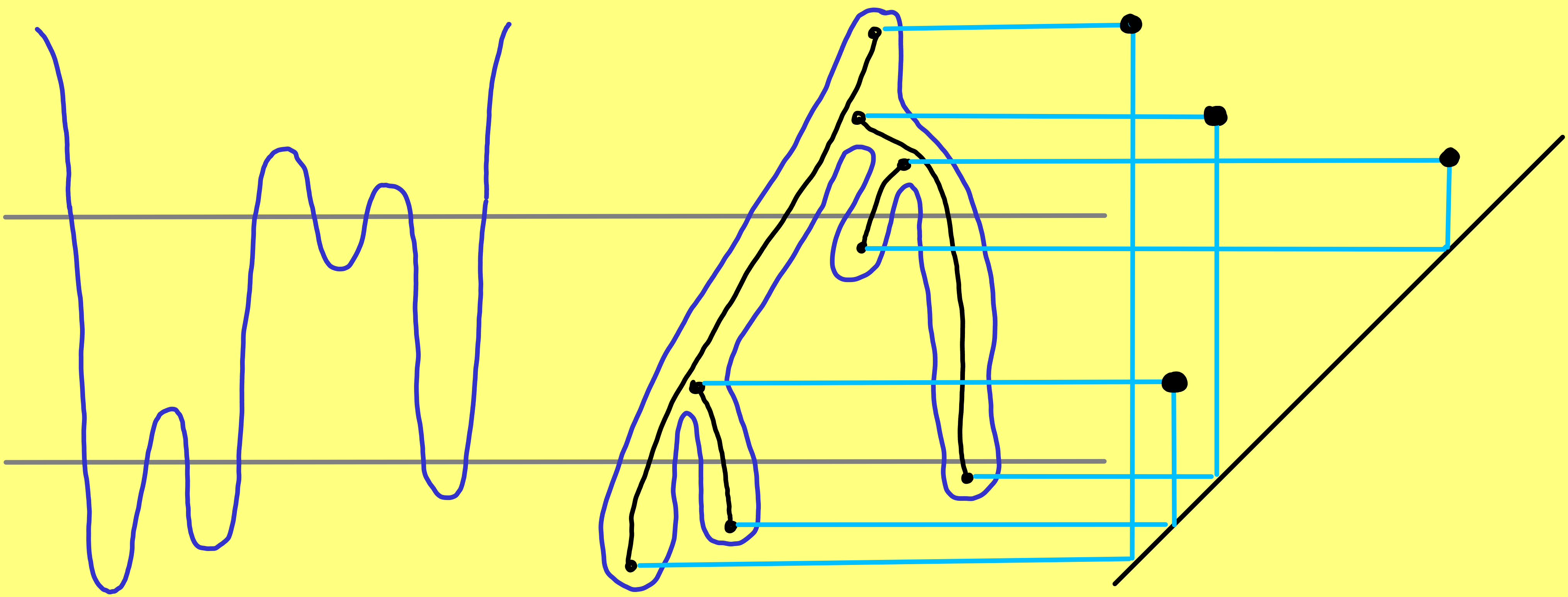

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persistence diagram

$\mathrm{Dgm}(f)$

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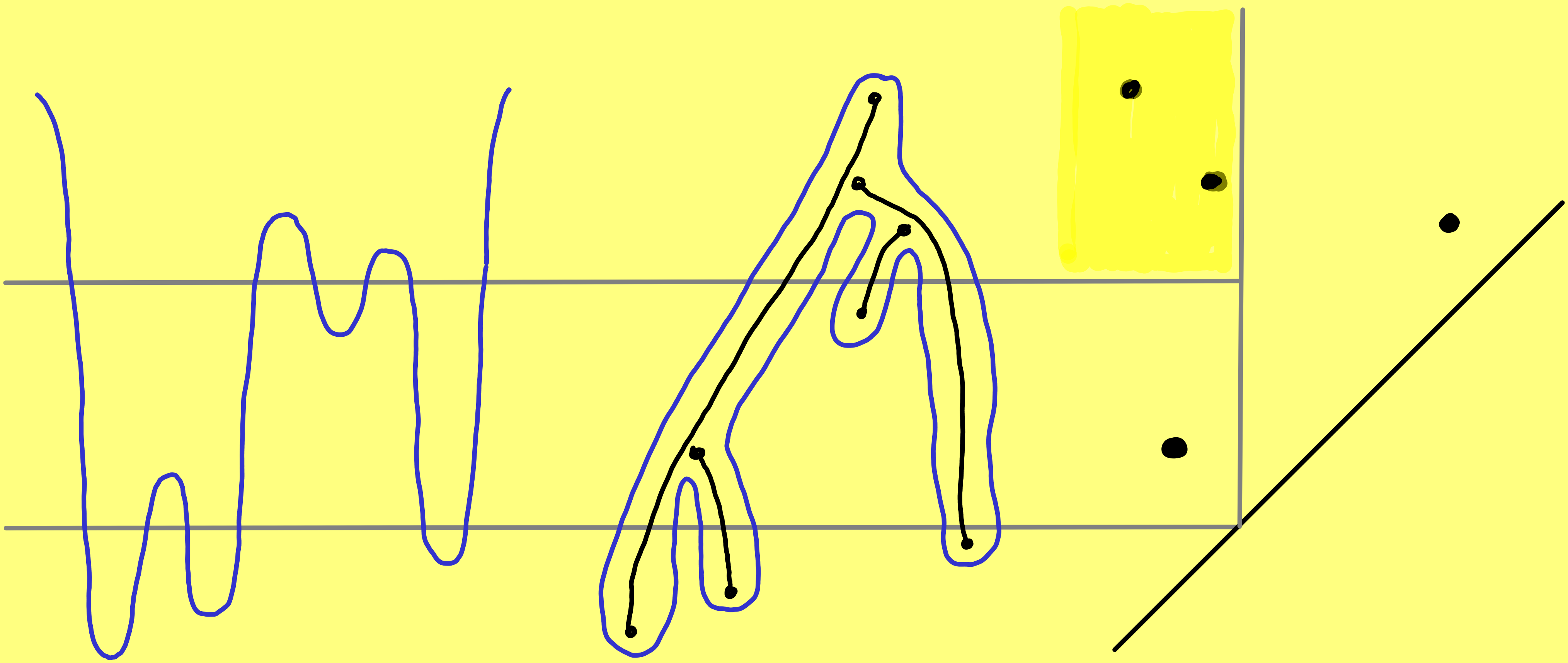

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merge tree

persistence diagram $\mathrm{Dgm}(f)$

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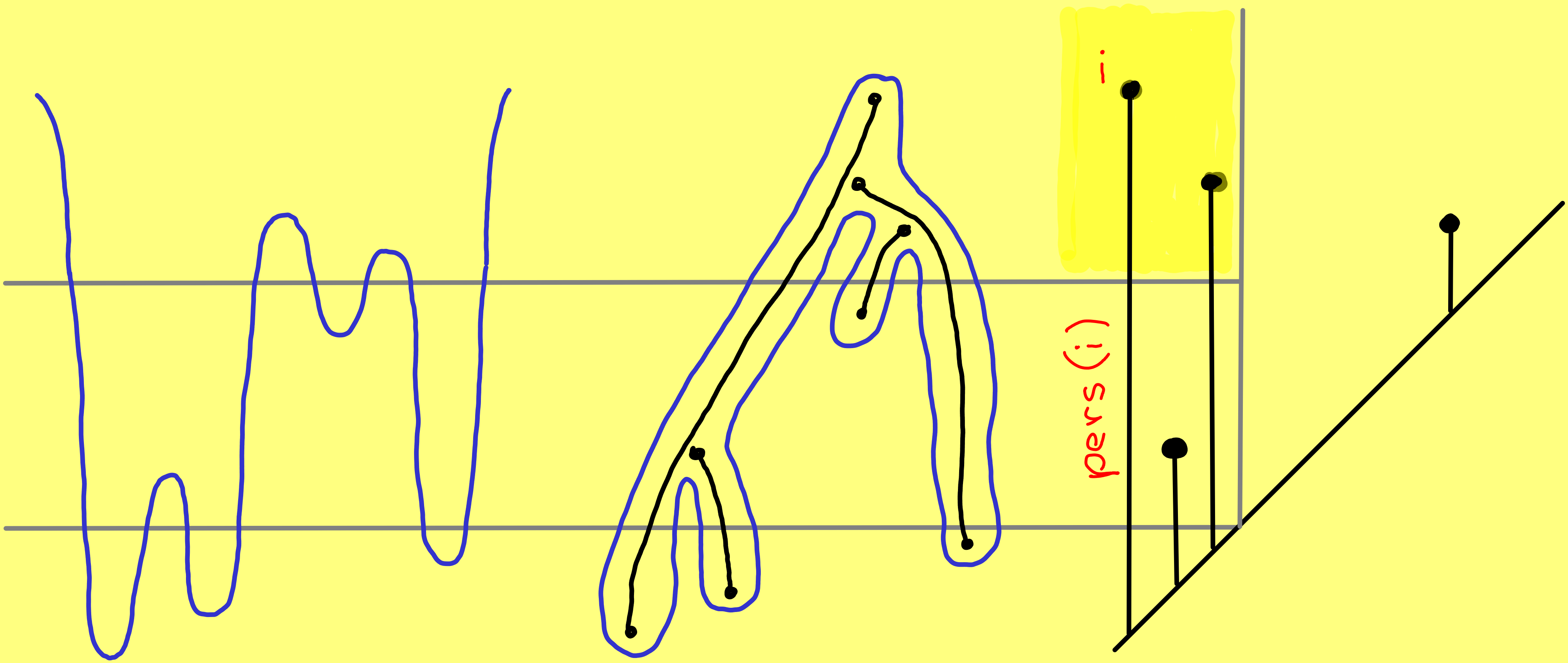

function

$f : \mathbb{S}^1 \to \mathbb{R}$

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$\mathrm{Dgm}(f)$

I.2 Total Absolute Variation

$$V(f) = \int_0^{2\pi} |f'(t)|\, dt$$

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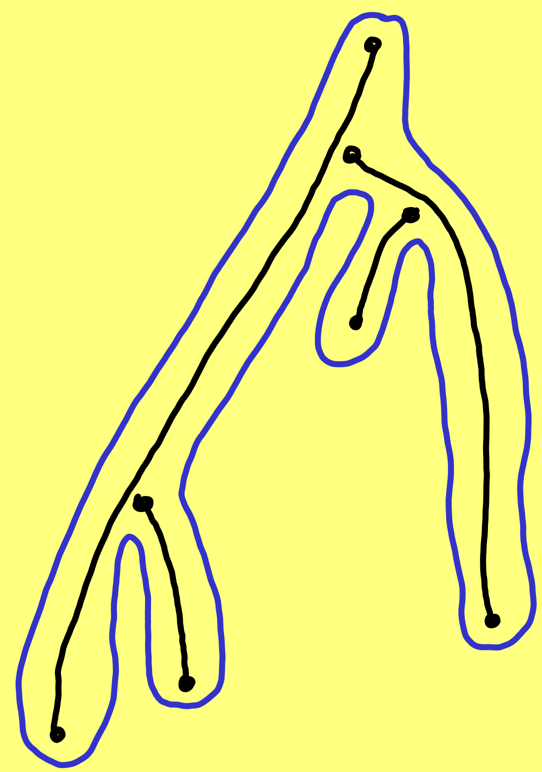
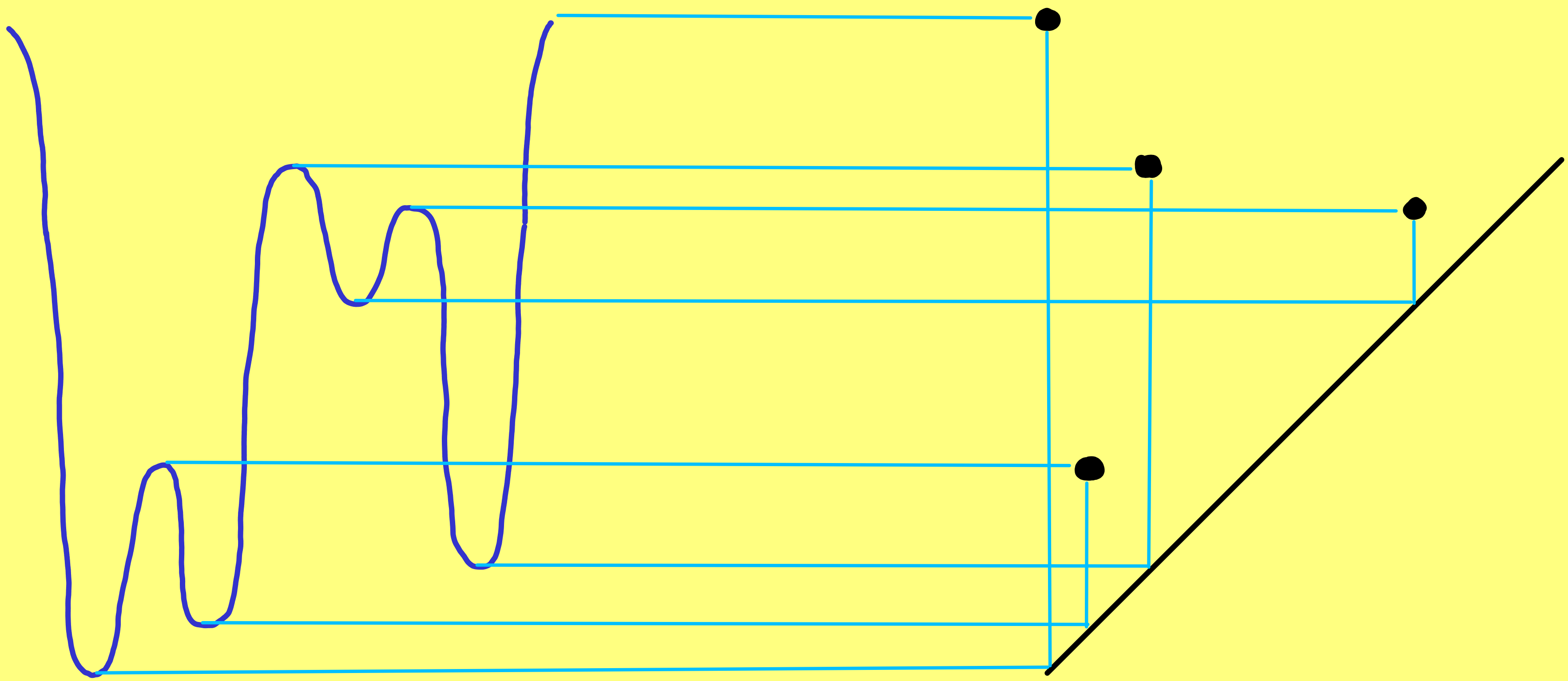


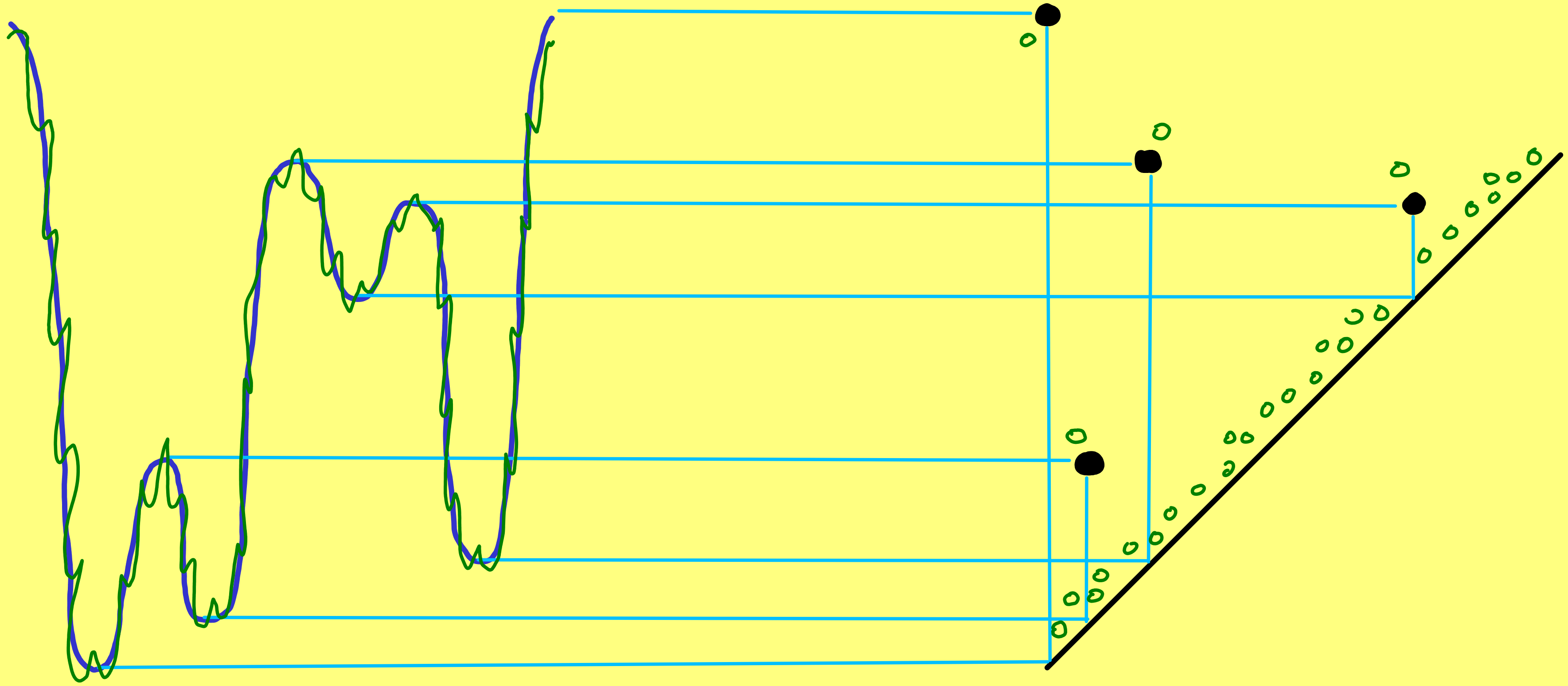
I.3 L_∞ - STABILITY

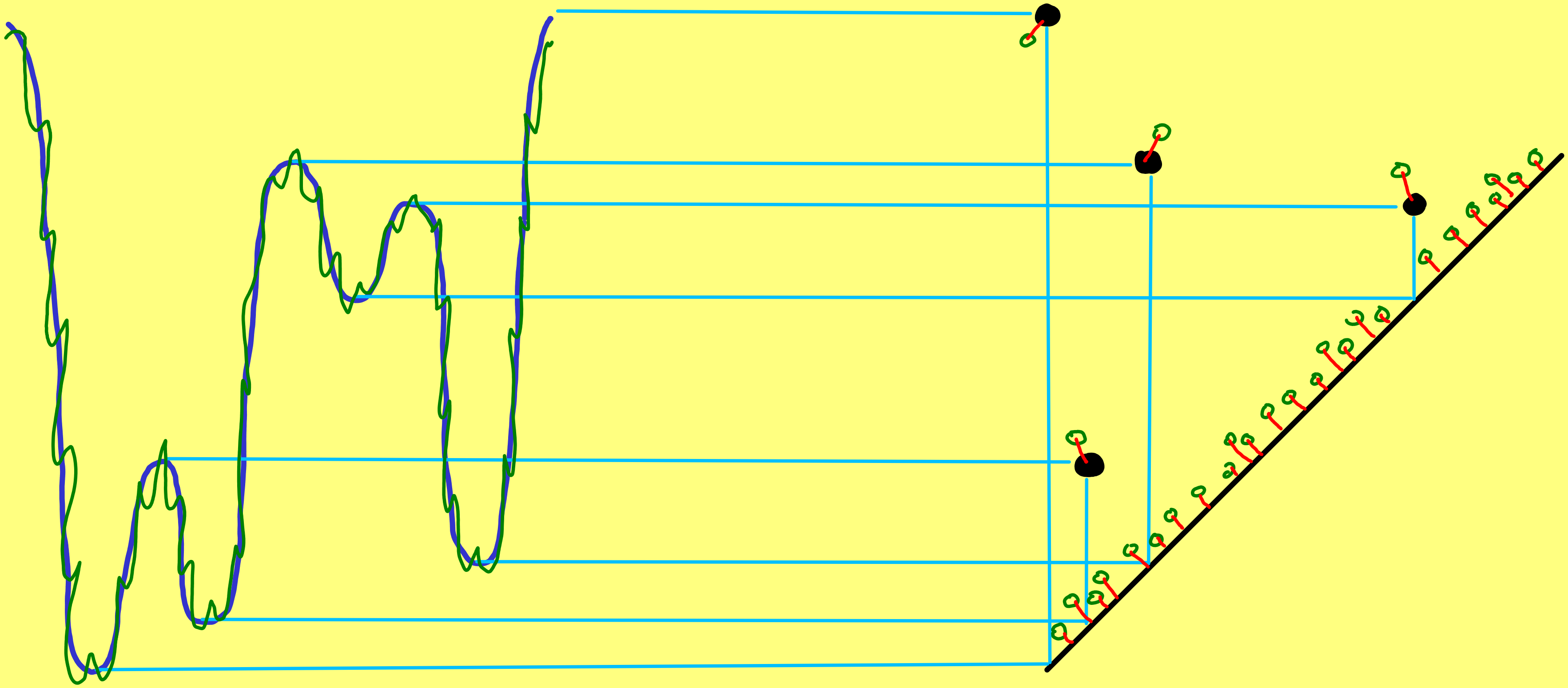
THM. (Cohen-Steiner, E, Harer 04)

For tame functions $f, g : \mathbb{X} \to \mathbb{R}$ the bottle-neck distance between their diagrams is bounded by the max-difference between the functions,

$$d_B(\mathrm{Dgm}(f), \mathrm{Dgm}(g)) \leq \|f - g\|_\infty .$$







$$d_B(\mathrm{Dgm}(f), \mathrm{Dgm}(g)) \leq \|f-g\|_\infty.$$

I.4 LIPSCHITZ

DEF. $f : \mathbb{S}^1 \to \mathbb{R}$ has Lipschitz constant C if $f(x) - f(y) \leq C\|x-y\|$.

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$\Longrightarrow$ total absolute variation is $V(f) \le 2C\pi$.

I.5 L_p-STABILITY

THM. (Cohen-Steiner, E, Harer, Mileyko 07)

Let $\mathbb{X}$ be a compact metric space and $f, g : \mathbb{X} \to \mathbb{R}$ two Lipschitz functions. Then there exists a constant k that depends on $\mathbb{X}$ and the Lipschitz constants of f and g such that

$$\left| \sum_{i \in \mathrm{Dgm}(f)} \mathrm{pers}(i)^p - \sum_{j \in \mathrm{Dgm}(g)} \mathrm{pers}(j)^p \right| \leq \mathrm{Const} \cdot \| f - g \|_\infty$$

for every integer $p \geq k + 1$.

I.5 L_p-STABILITY

For $\mathbb{X} = \mathbb{S}^1$: $k = 1$.

Hence

$$\left| \sum_{i \in Dgm(f)} pers(i)^2 - \sum_{j \in Dgm(g)} pers(j)^2 \right| \leq Const \cdot \|f - g\|_\infty$$

WHY NOT $p = 1$?

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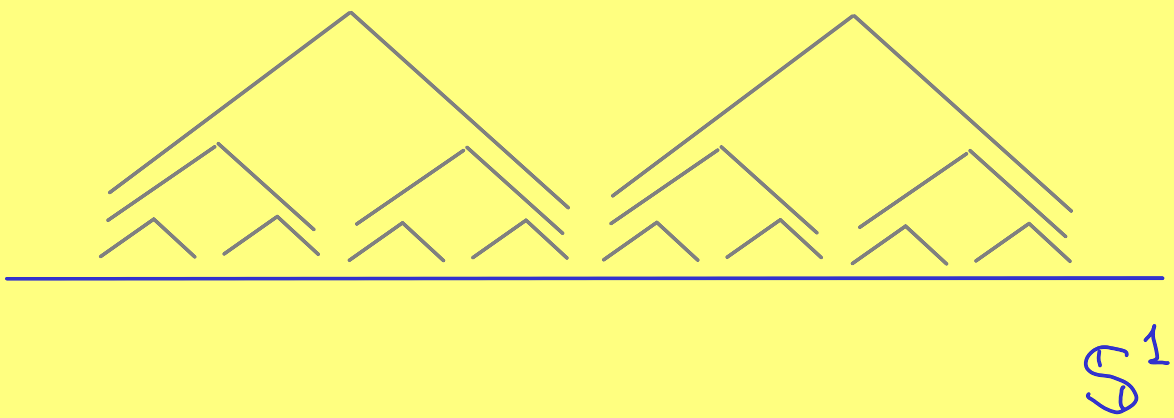

II. Motivation: Somitogenesis

work by Olivier Pourquié

Mary-Lee Dequéant

II.1 SEGMENTATION of vertebrate body plan

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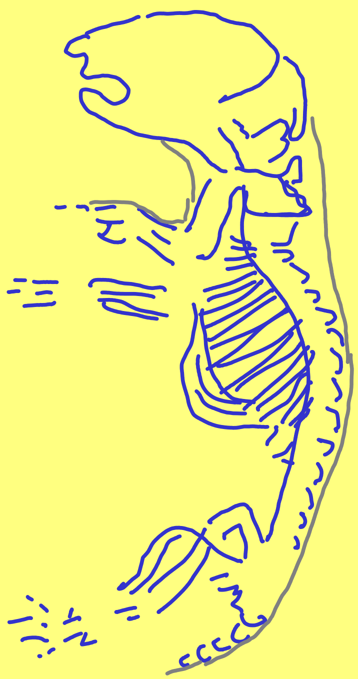
adult mouse



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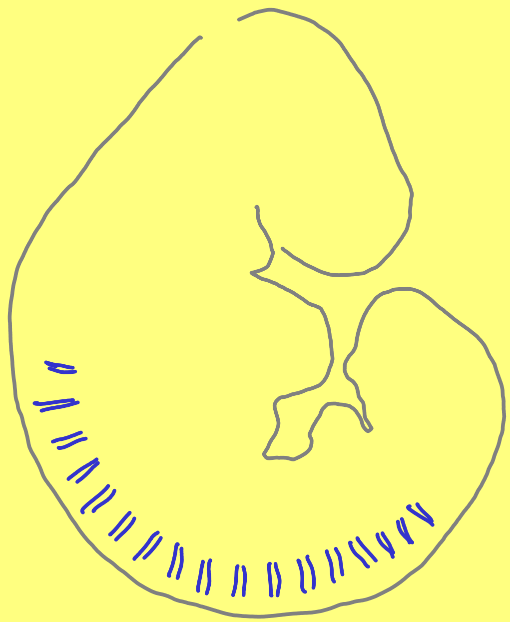
adult mouse

mouse embryo



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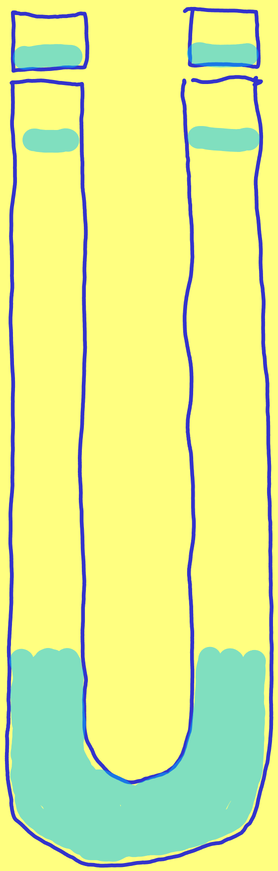

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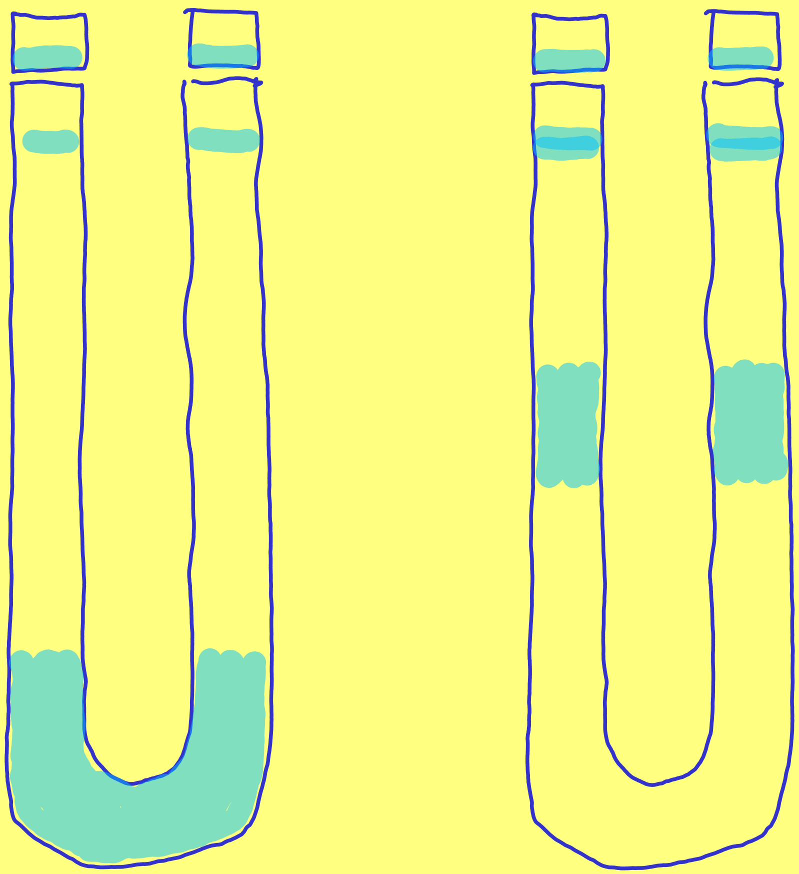

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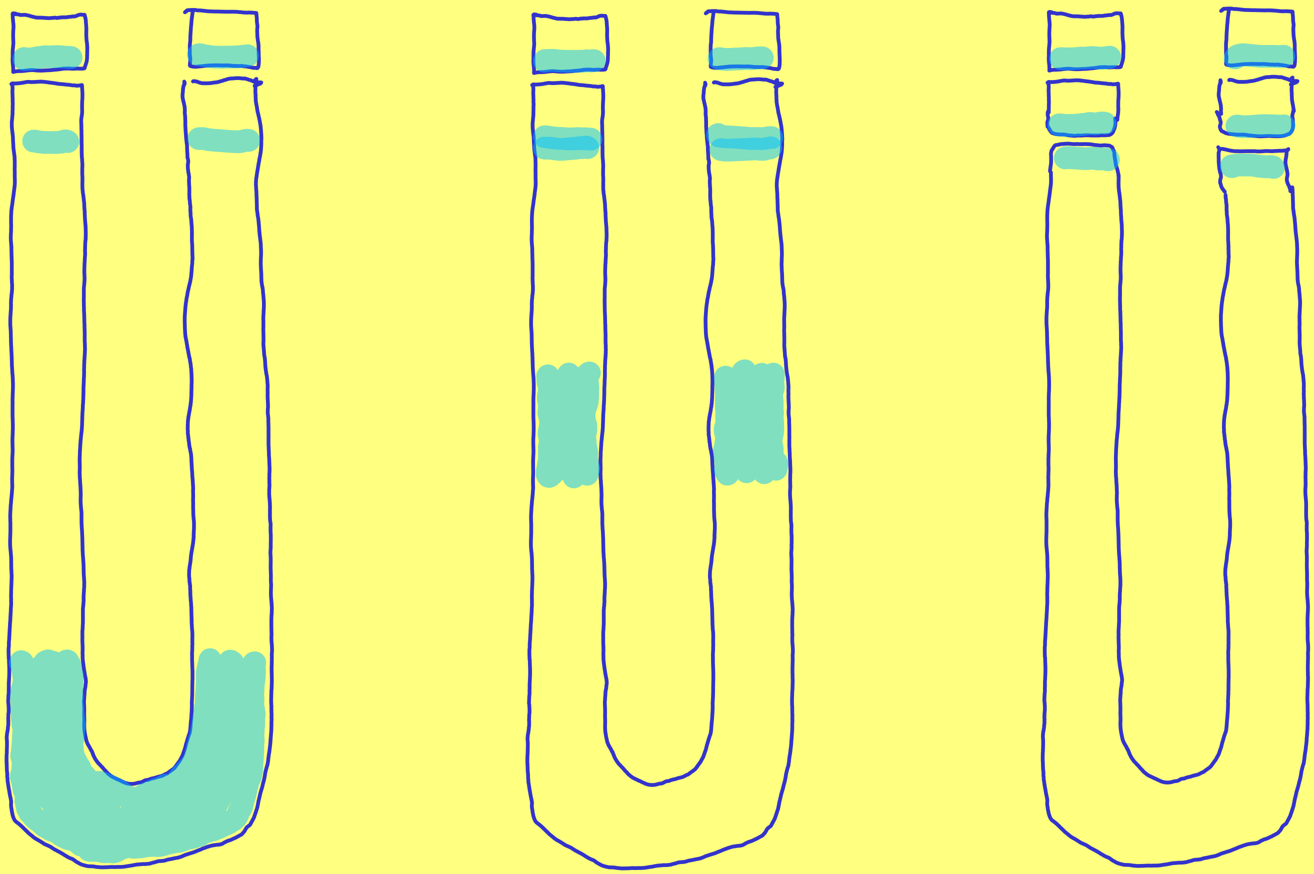
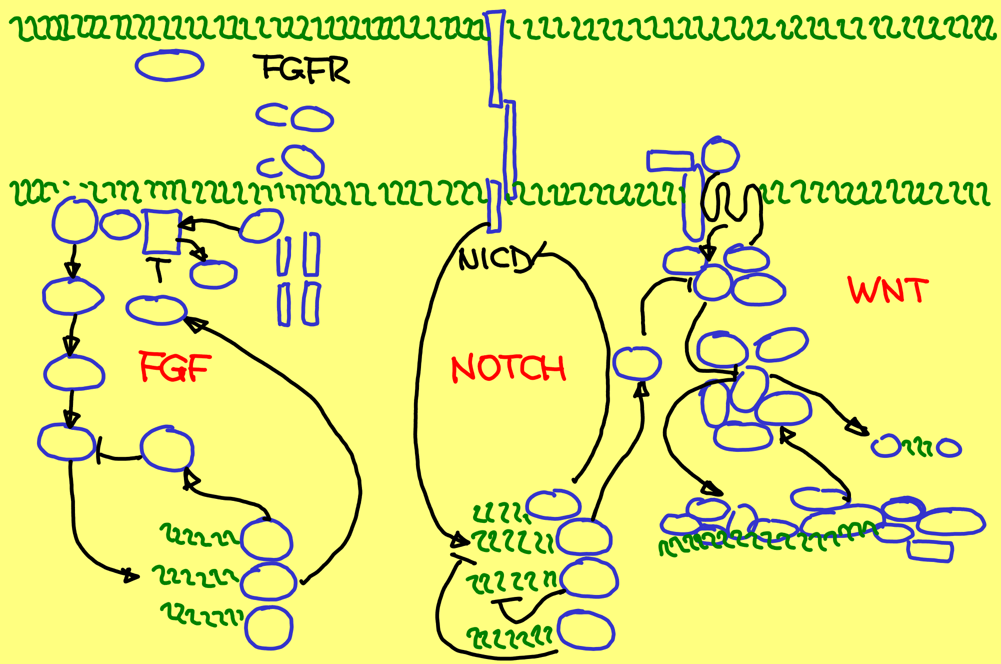


II.3 THE CLOCK



proposed model

II.4 Cyclic Genes

... time series microarray analysis

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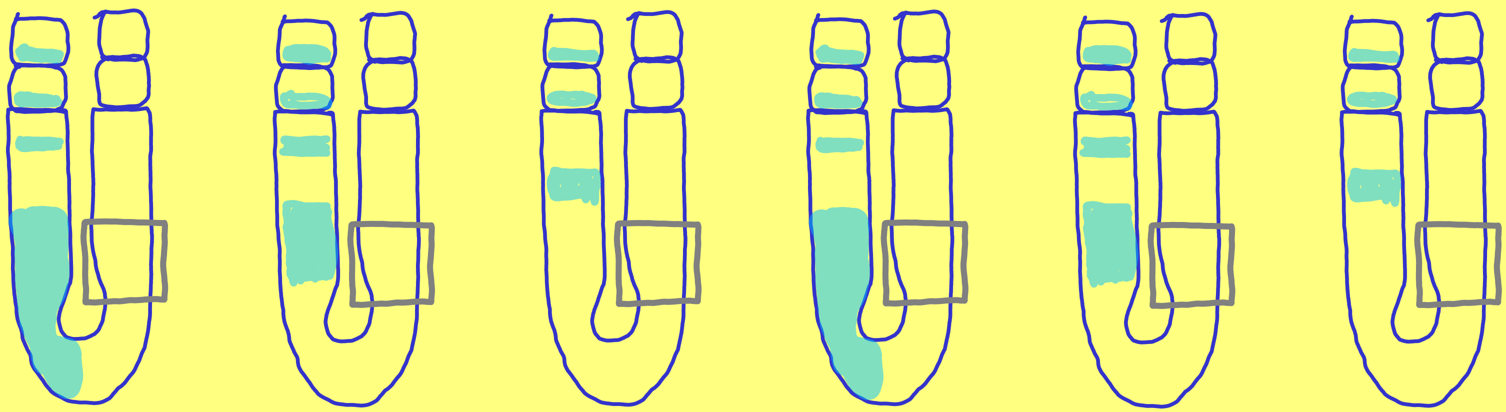

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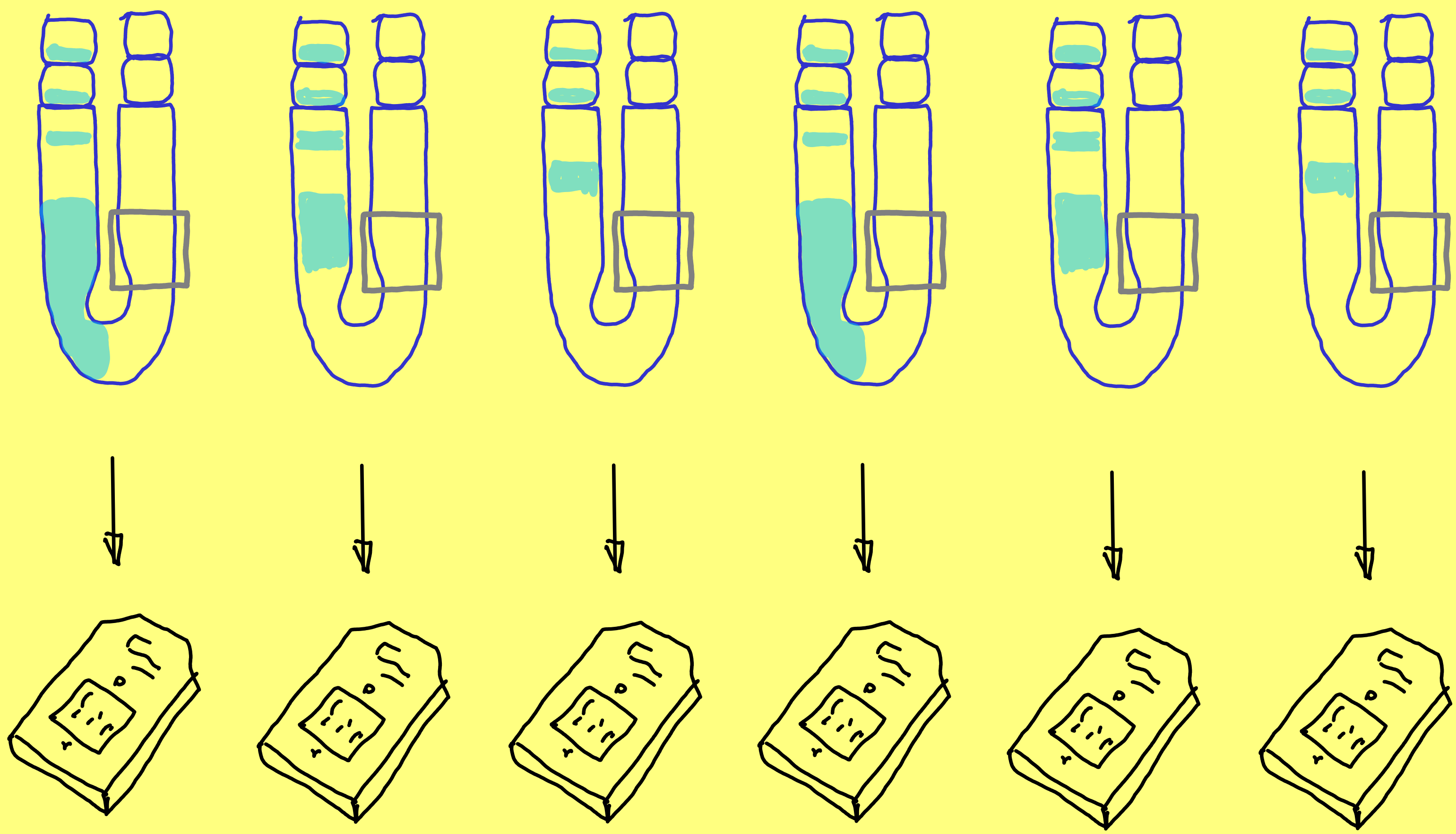
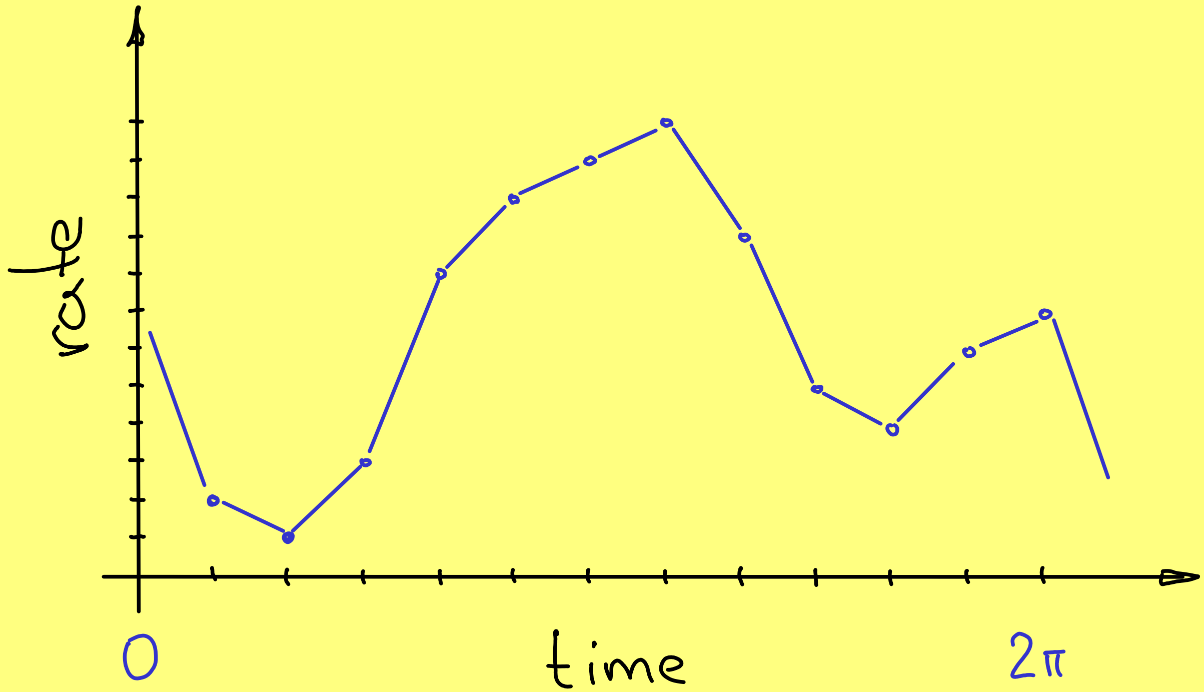


III. Methods: Measures

III.1 Data Normalization

pts. in time, expression rates $\rightarrow$ ranks



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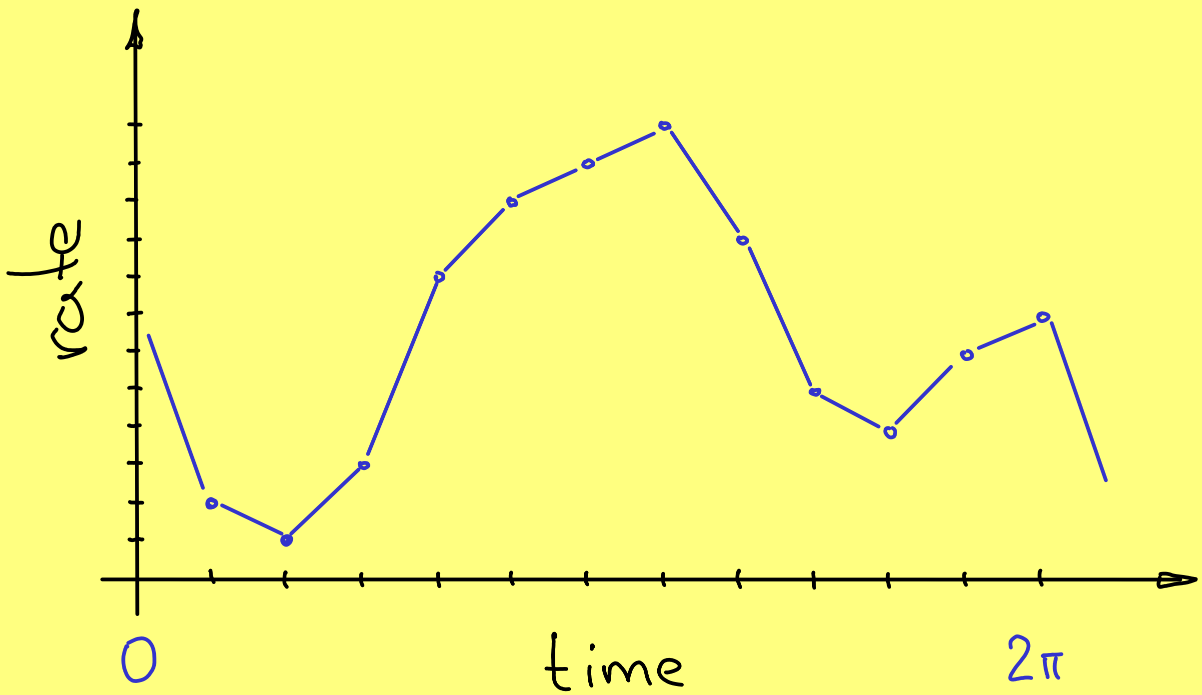

normalized to $\operatorname{amp}(f) = \max_x f(x) - \min_x f(x) = 1$

III.2 Simplification

Def. (E, Morozov, Pascucci 06) An ε-simplification of f is a function $f_\varepsilon : \mathbb{X} \to \mathbb{R}$ with $\|f - f_\varepsilon\|_\infty \leq \varepsilon$ whose diagram $\mathrm{Dgm}(f_\varepsilon)$ is same as $\mathrm{Dgm}(f)$ without points of persistence at most ε.

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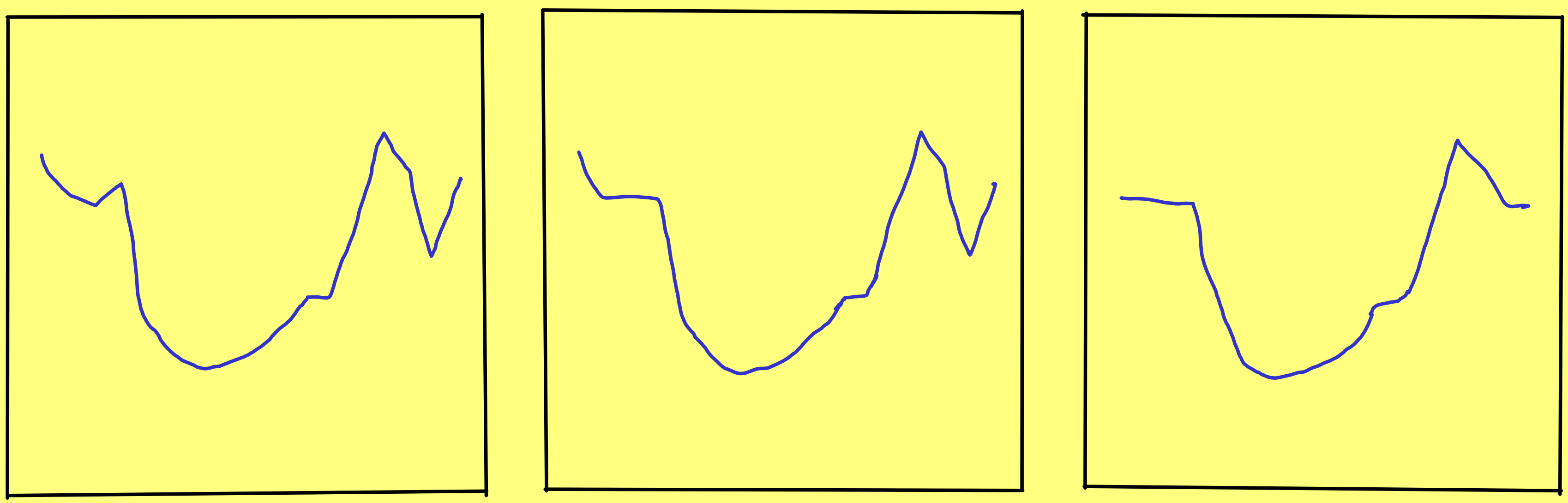

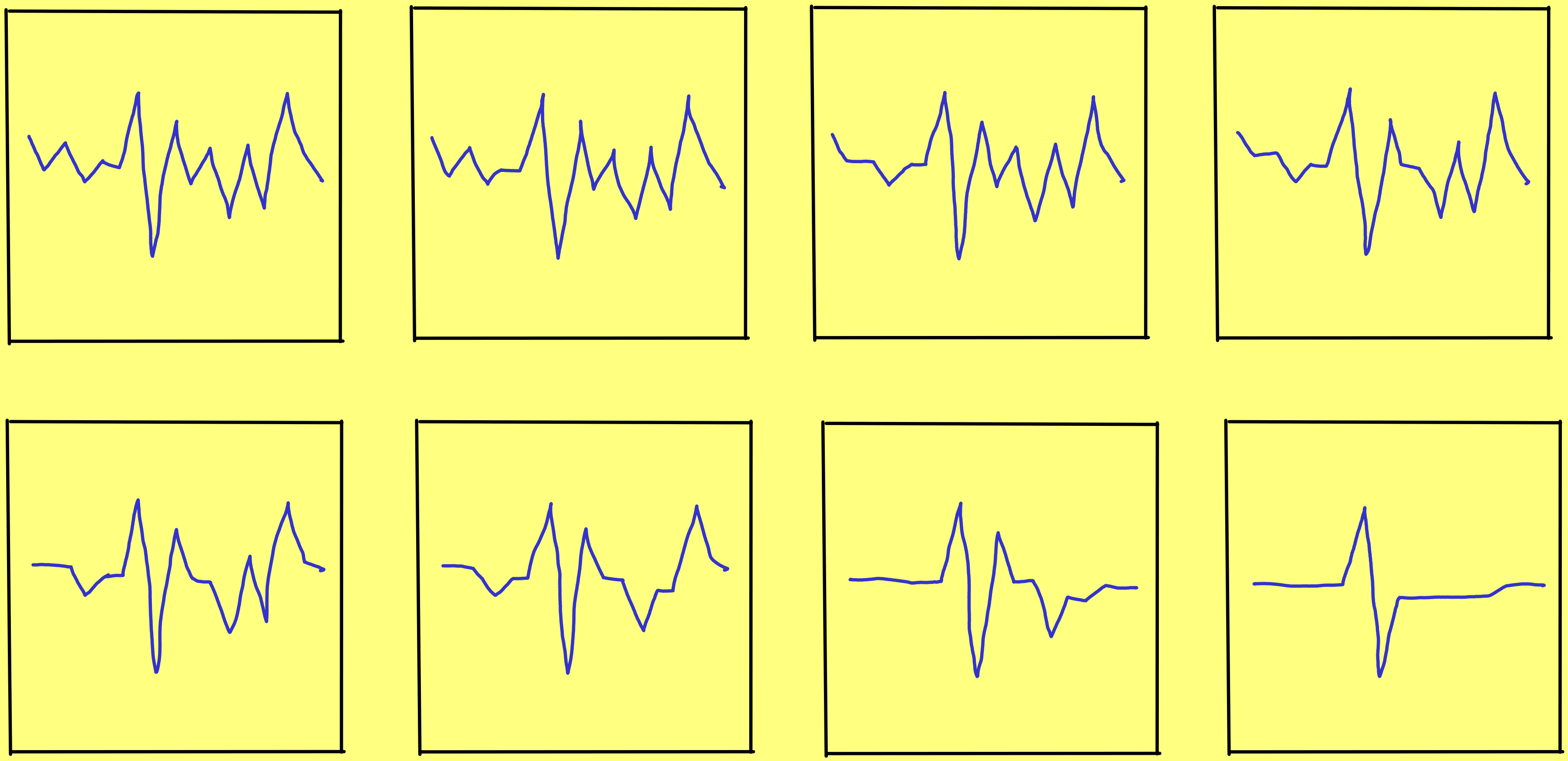

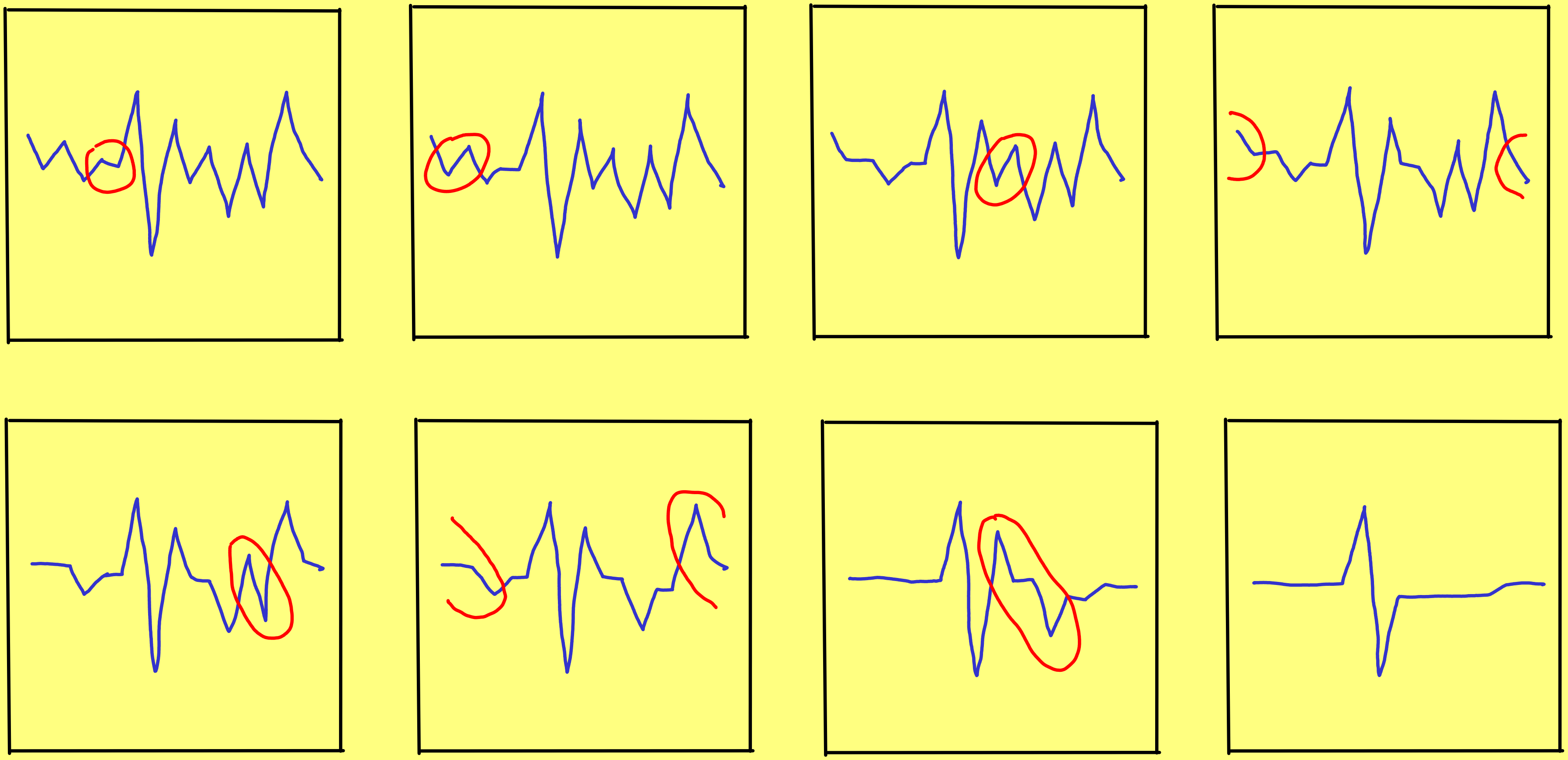

III.3 Periodicity Measures

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$$M_2(f) = \int_{\varepsilon=0}^{1} M_1(f_\varepsilon)\, d\varepsilon = \sum_i \text{pers}(i)^2$$

etc.

III.3 Periodicity Measures

$$f : \mathbb{S}^1 \to \mathbb{R}$$

not stable

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$$M_1(f) = \int_{\varepsilon=0}^{1} M_0(f_\varepsilon)\, d\varepsilon = \sum_i \mathrm{pers}(i)$$

stable

$$M_2(f) = \int_{\varepsilon=0}^{1} M_1(f_\varepsilon)\, d\varepsilon = \sum_i \mathrm{pers}(i)^2$$

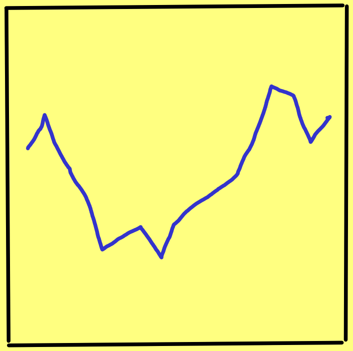
etc.

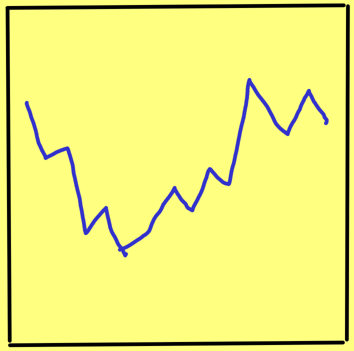
IV. Results: Rankings

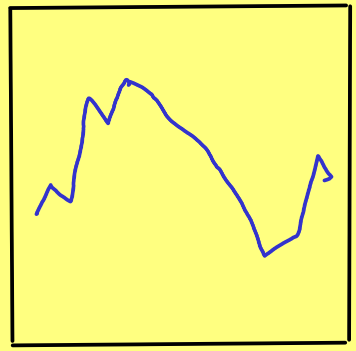
IV.1 VERIFIED - 30

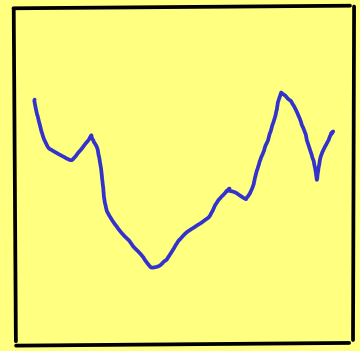
(biologically confirmed to participate in the periodic process of somite development)

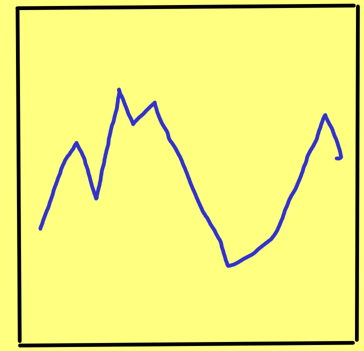
Dkk1	Tnfrsf19	Hes1	Axin2	Hspg2
Myc	Hes5	Dact1	Sp5	Efna1
Bcl2l11	a-Tnfrsf19	Lfng	Spry2	Klf10
s-Dsp	Hey1	Plxdc2	Nudt13	Bcl9l
Id1	Has2	5-Nrarp	Dsp	Phlda1
Arfl4	Nkd1	6-Nrarp	x-Cyr61	a-Cyr61


Dkk1

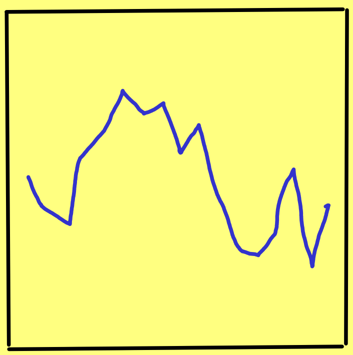

Tnfrsf19

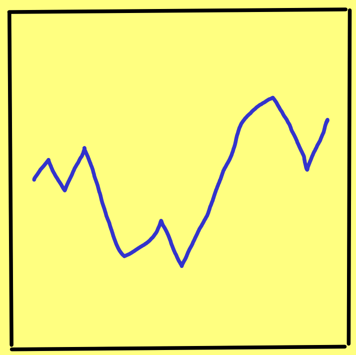

Hes1

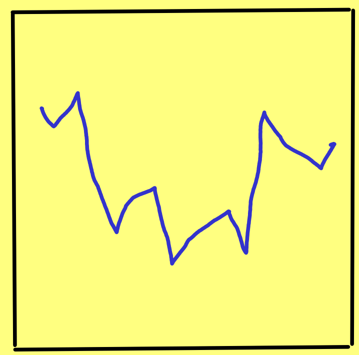

Axin2

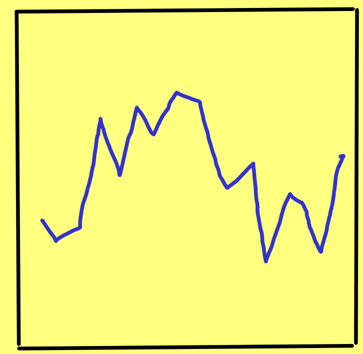

Hspg2


Myc

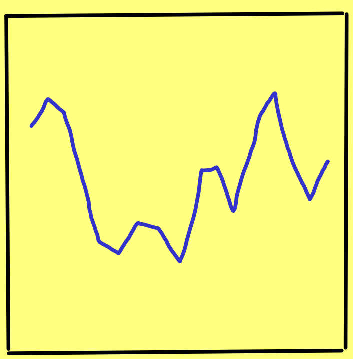

Hes5

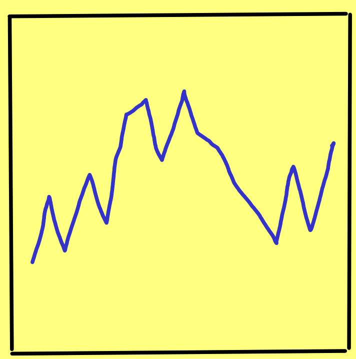

Dact1

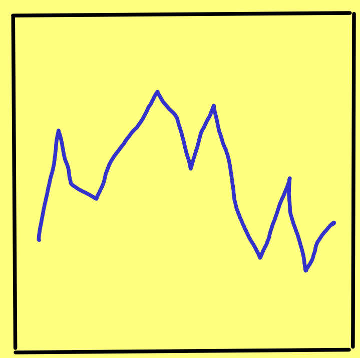

Sp5

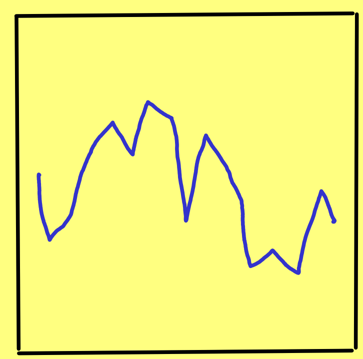

Efna1

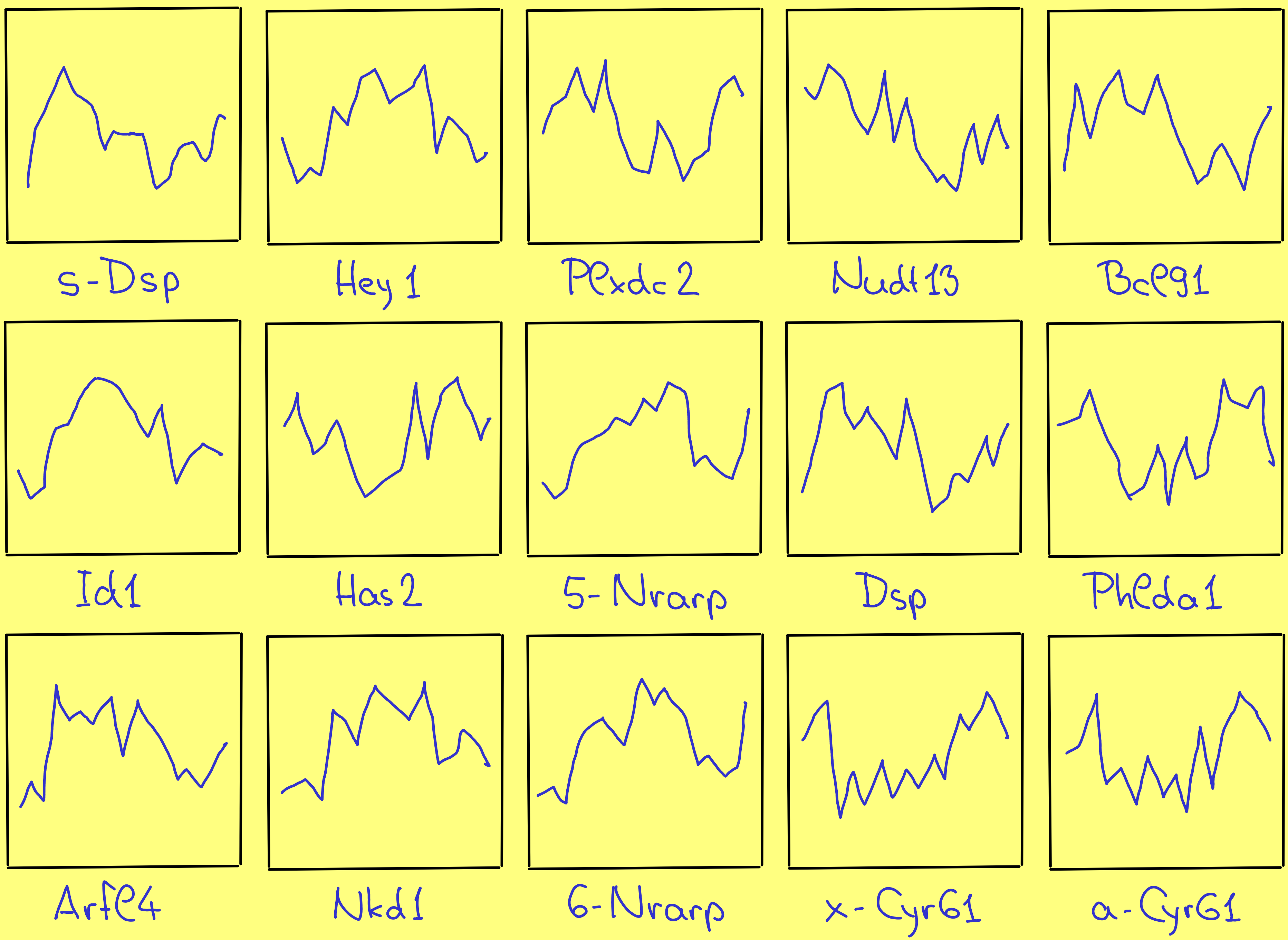

Bcl2l11


a-Tfnrsf19


Lnfg


Spry2


Klf10

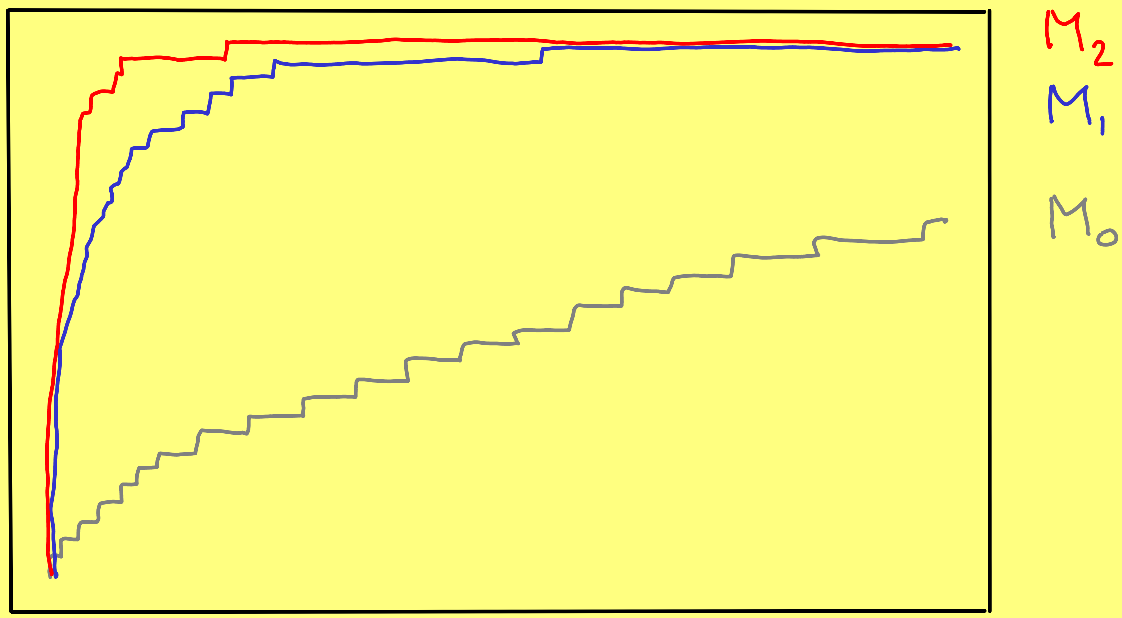

s-Dsp
Hey 1
Plxdc 2
Nudt13
Bcl9l
Id1
Has 2
5-Nrarp
Dsp
Phlda1
Arl4
Nkd1
6-Nrarp
x-Cyr61
a-Cyr61

IV.2 Internal Comparison

	M_1	M_2	M_3	M_4	avg
Dkk1	1	1	1	1	1
Tnfrsf19	12	2	2	2	5
Hey1	23	12	9	9	13
Nudt13	882	170	104	83	310
Arfl4	302	86	74	68	133
...	...	...	...	...	...
avg	250	109	104	117	145

IV.2 Internal Comparison

ROC Curves



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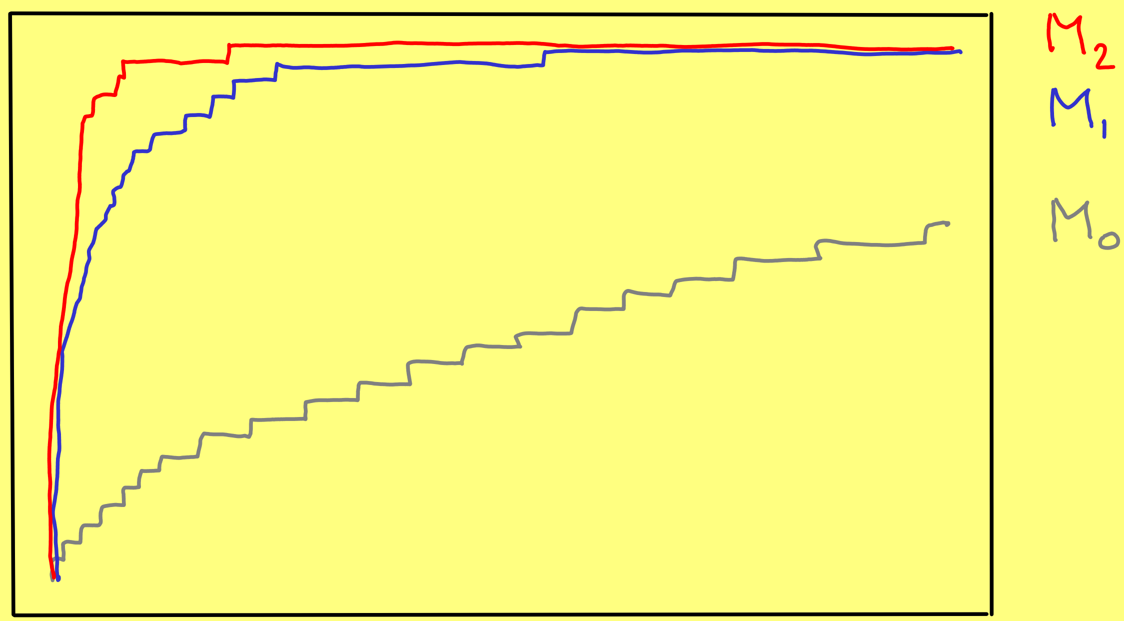

	M_0	M_1	M_2	M_3	M_4	max
Area	4.42	9.75	10.18	10.19	10.15	10.50

IV.2 Internal Comparison

Promising Candidates

	M_1	M_2	M_3	M_4	L
Tnfrsf9	5	4	4	6	8
Ptpn11	8	6	6	7	22
Mtm1	9	7	5	3	15
Stom	7	8	12	16	299
Star	6	9	11	13	39
...	...	...	...	...	...

IV.3 External Comparison

	1 + 4 Methods	
L	Lomb-Scargle	Stowers
P	Phase Consistency	Dallas
A	Address Reduction	Marie Curie
C	Cyclohedron Test	Berkeley
S	Stable Persistence	Duke

IV.3 External Comparison

	1 + 4 Methods	
L	Glynn, Hattem, Mishegian	Stowers
P	Kudlicki, Rowicka	Dallas
A	Ahnert, Fink	Marie Curie
C	Morton, Pachter, Shiu, Sturmfels	Berkeley
S	Edelsbrunner, Mileyko	Duke

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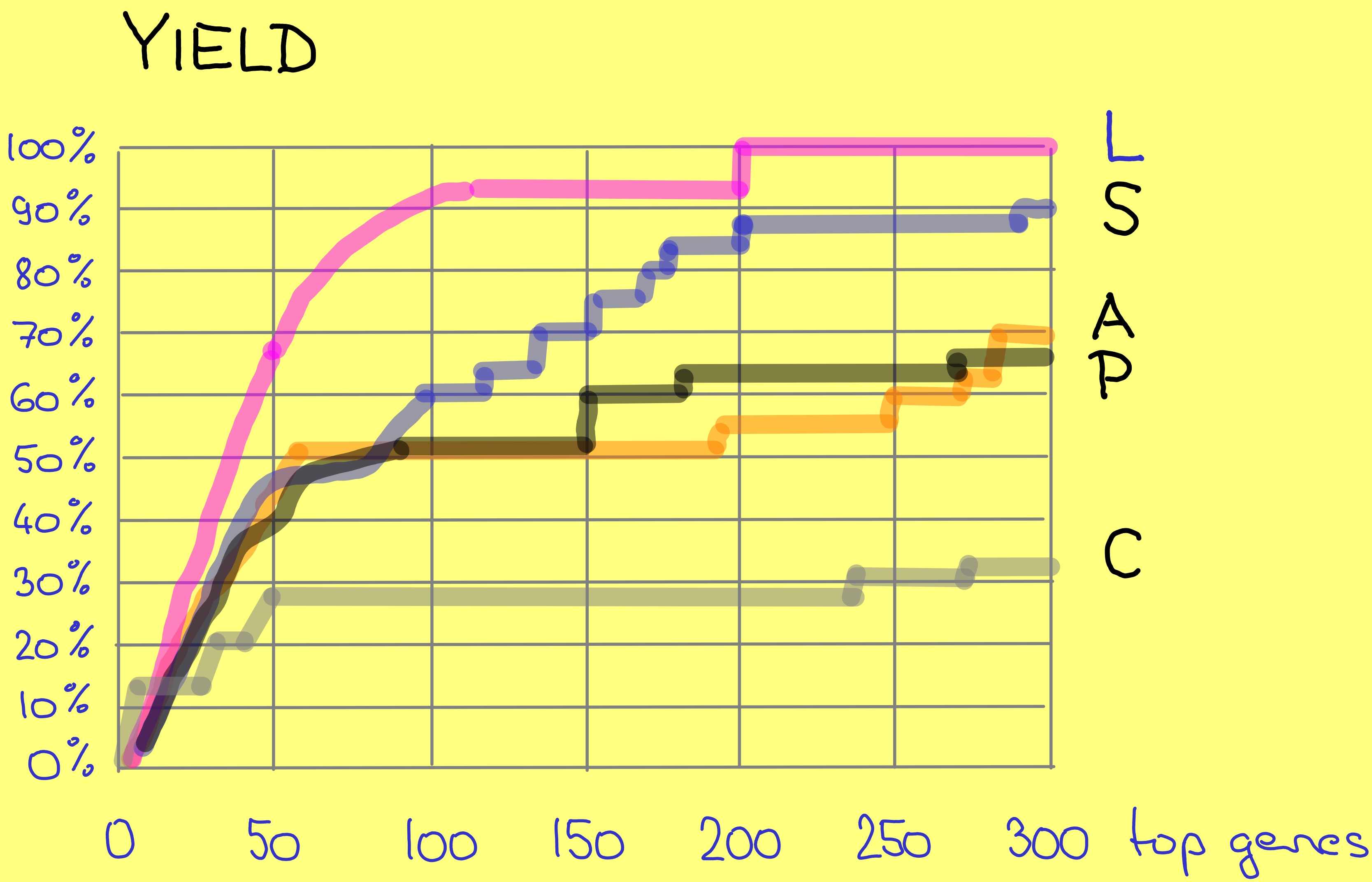

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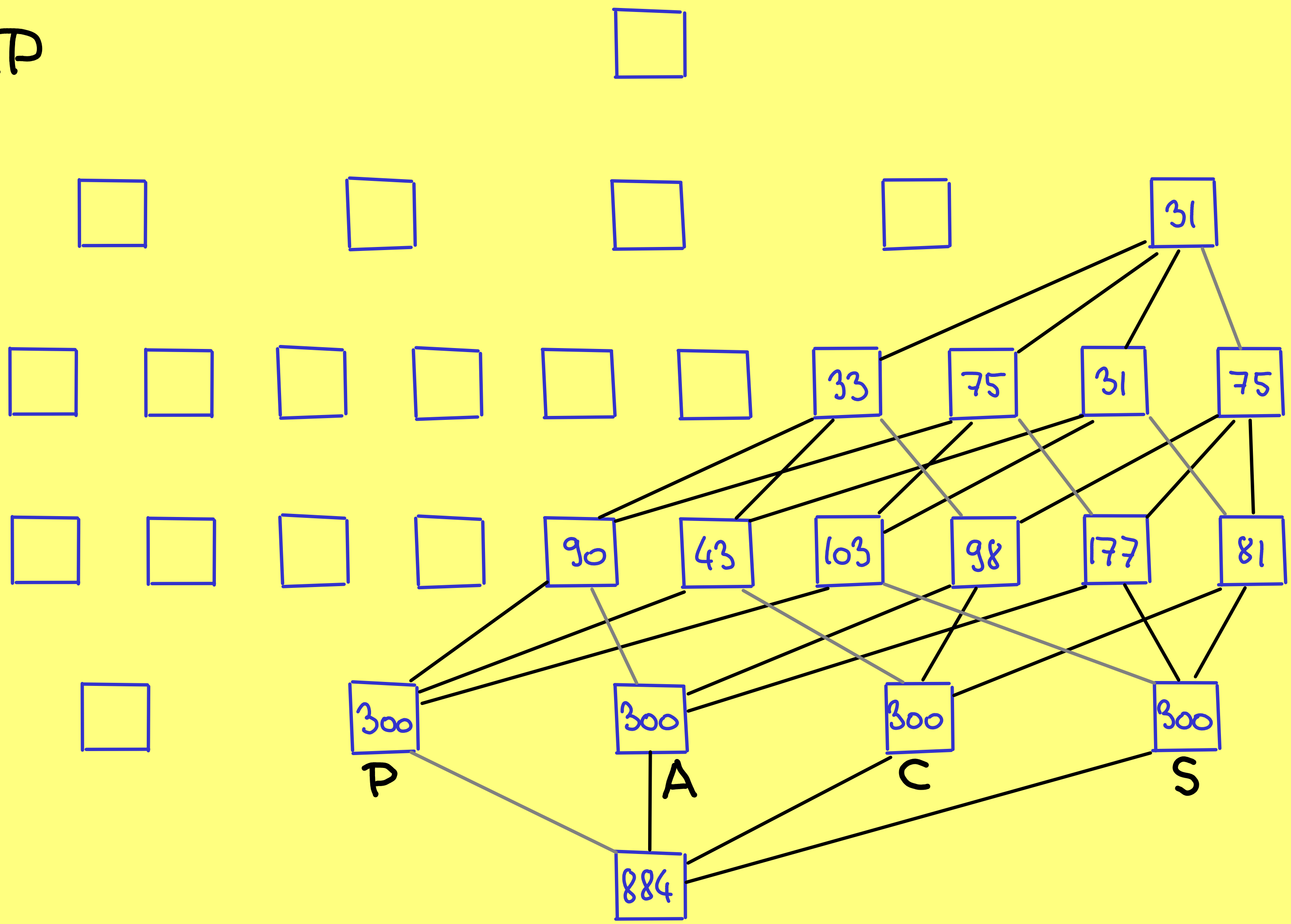
Overlap



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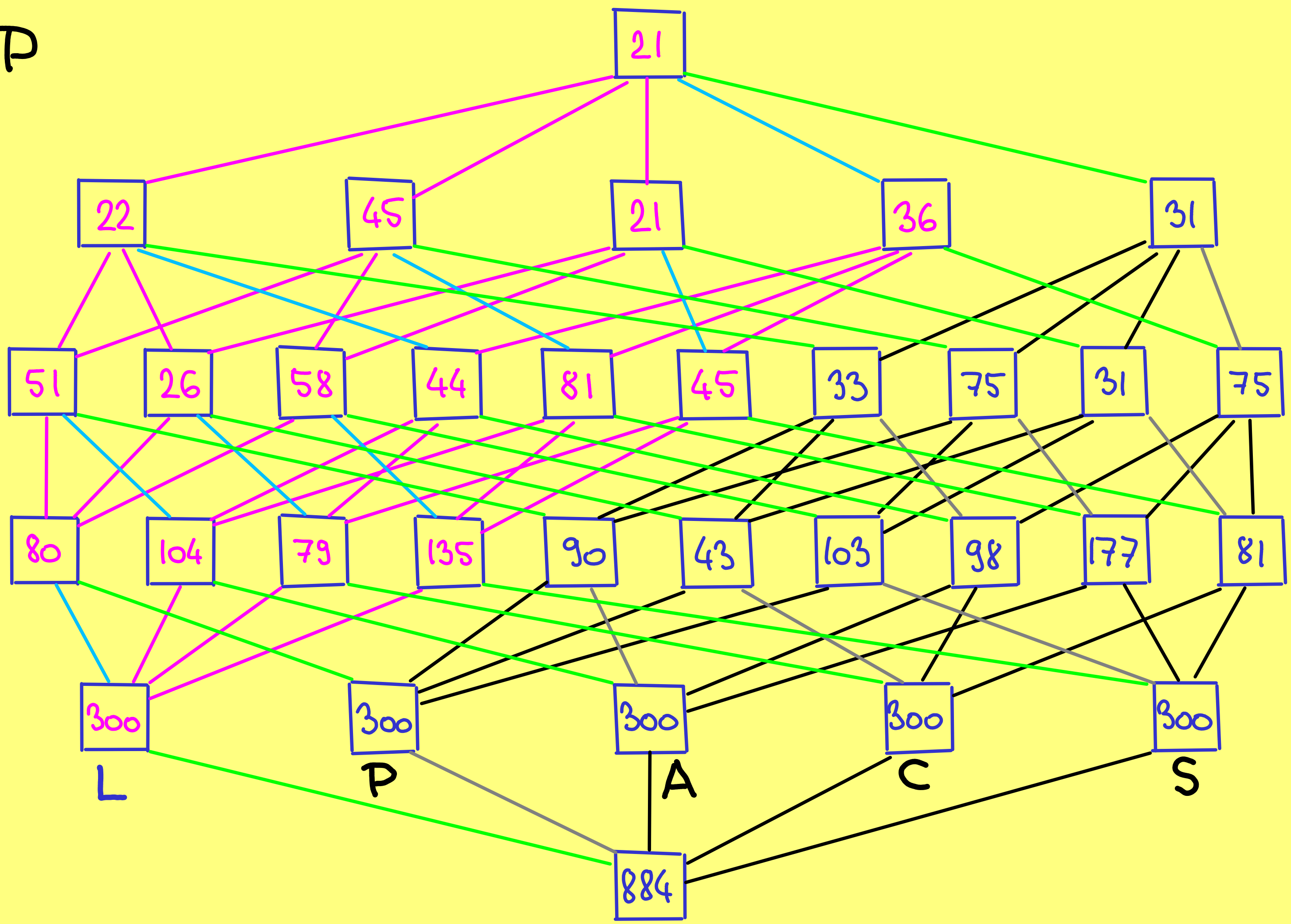

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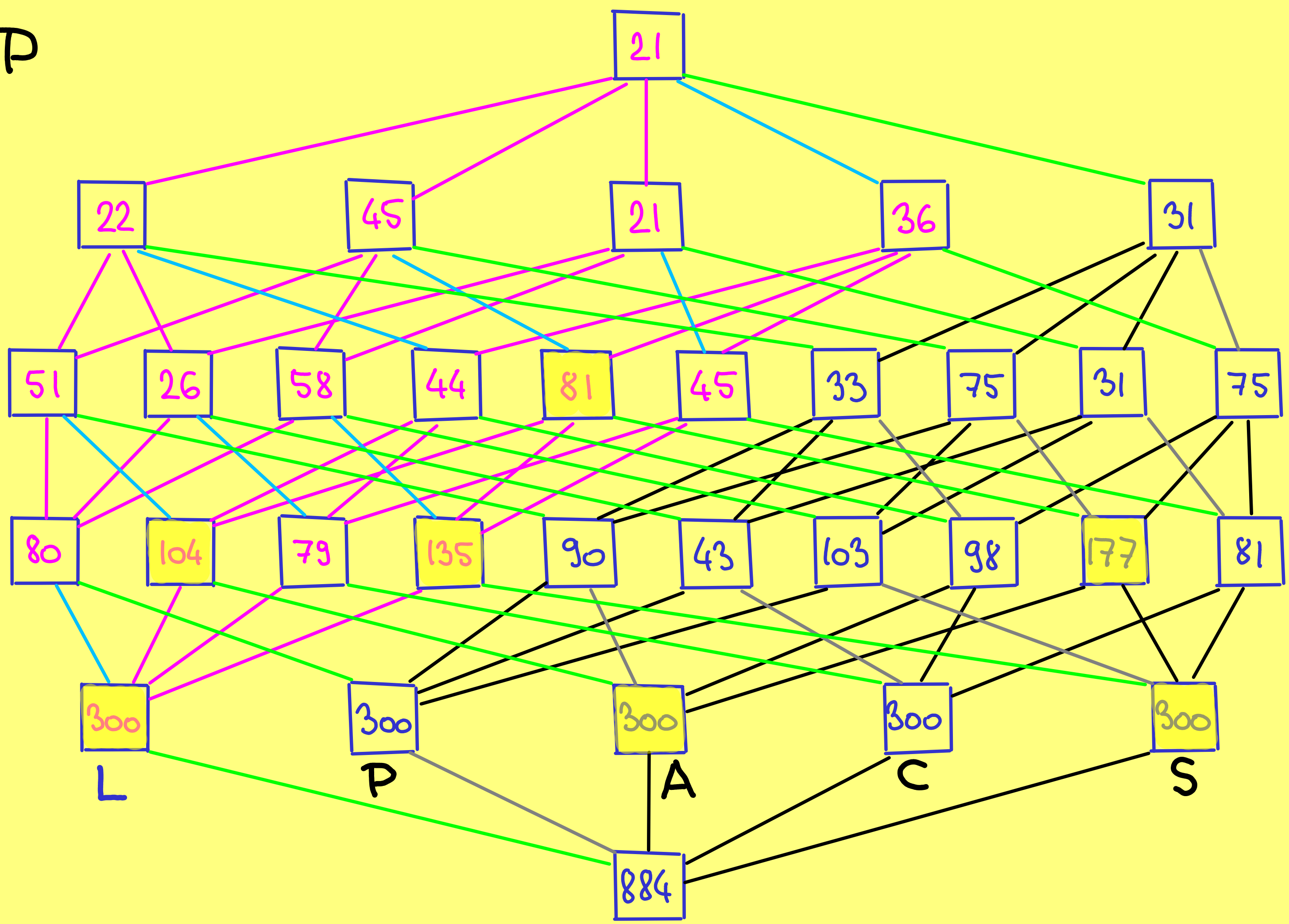

IV.3 · External Comparison

WNT Cluster

		L	P	A	C	S
Wnt cyclic genes	validated					
	candidates					

THANK YOU