Models (and principles) of early immune recognition and antagonism

G.A.B (NIH)

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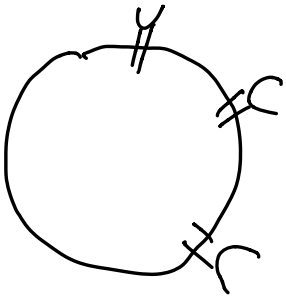
Early detection: 1st 5 minutes

T cells .

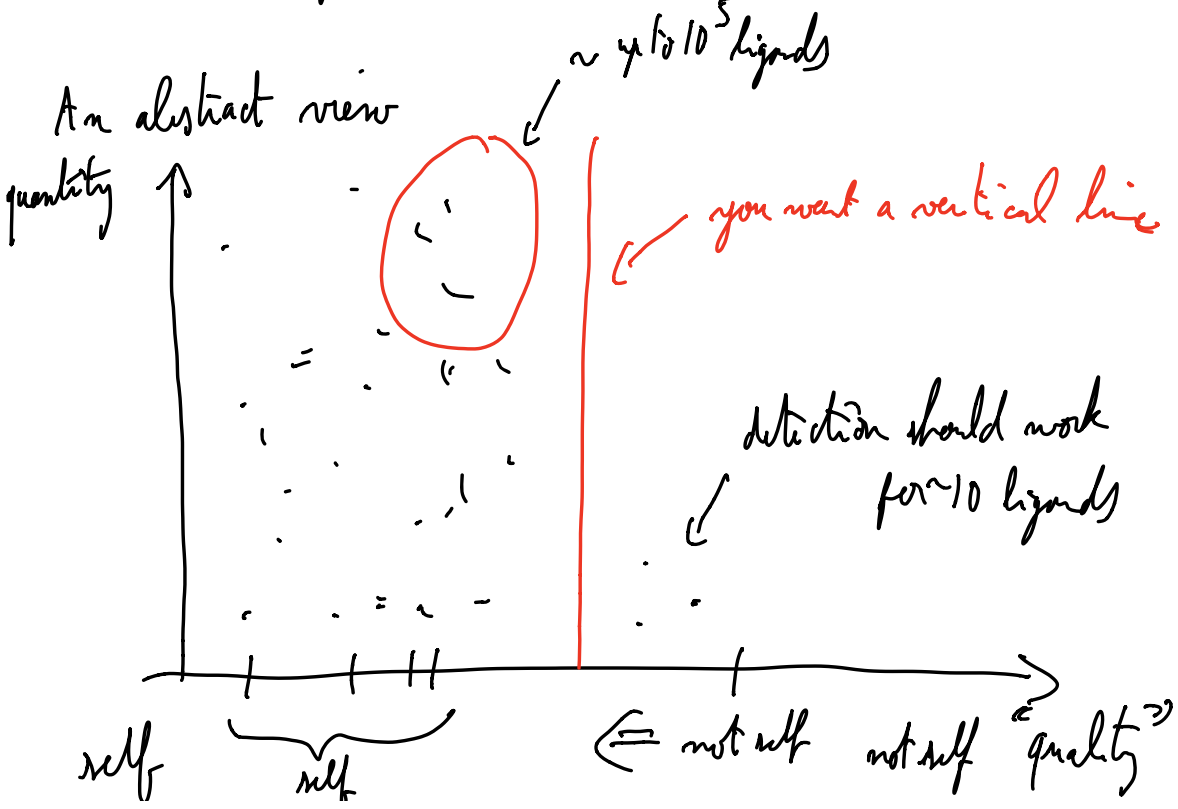


← scan for environment

"ligands"

30 000 receptors

Problem: self vs not self .



Here quality ≡ binding time of ligand to receptor

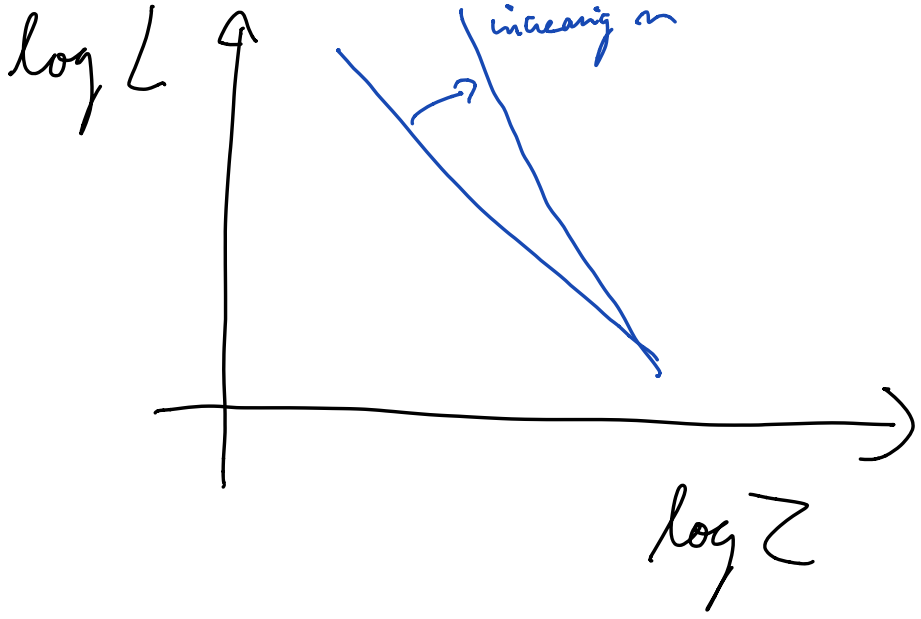
threshold around 4s.

Vertical line: tough problem.

Imagine the following

$$R + L \underset{Z^{-1}}{\rightleftharpoons} C \qquad \text{Measure } C \sim LZ$$

L "competes" for Z



Mc Keithan 95' KPR

LZ^m

G.A.B and Gunawi $m \sim 100$ or 20 + too slow.

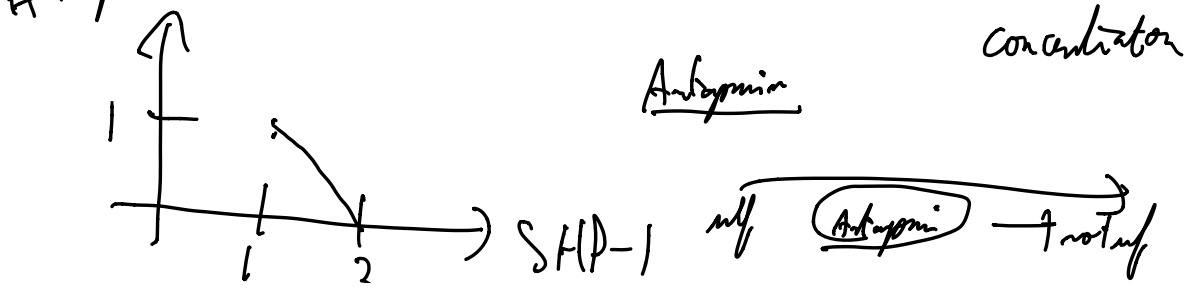
⇒ very complex models ($\sim$ 100 equations, species)

Explains a lot of other features such as:

- time of response ($\sim$ 5 min) + non monotonic dependency of response time

-

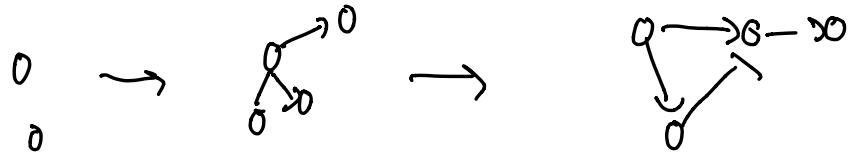
- "digital" vs "analog" effect



How to make a theory of this ?

Tool : "in silico" evolution

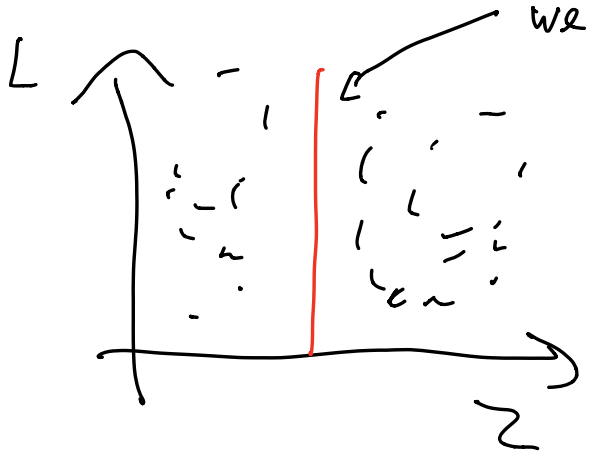
(machine learning)



"fitness" increase

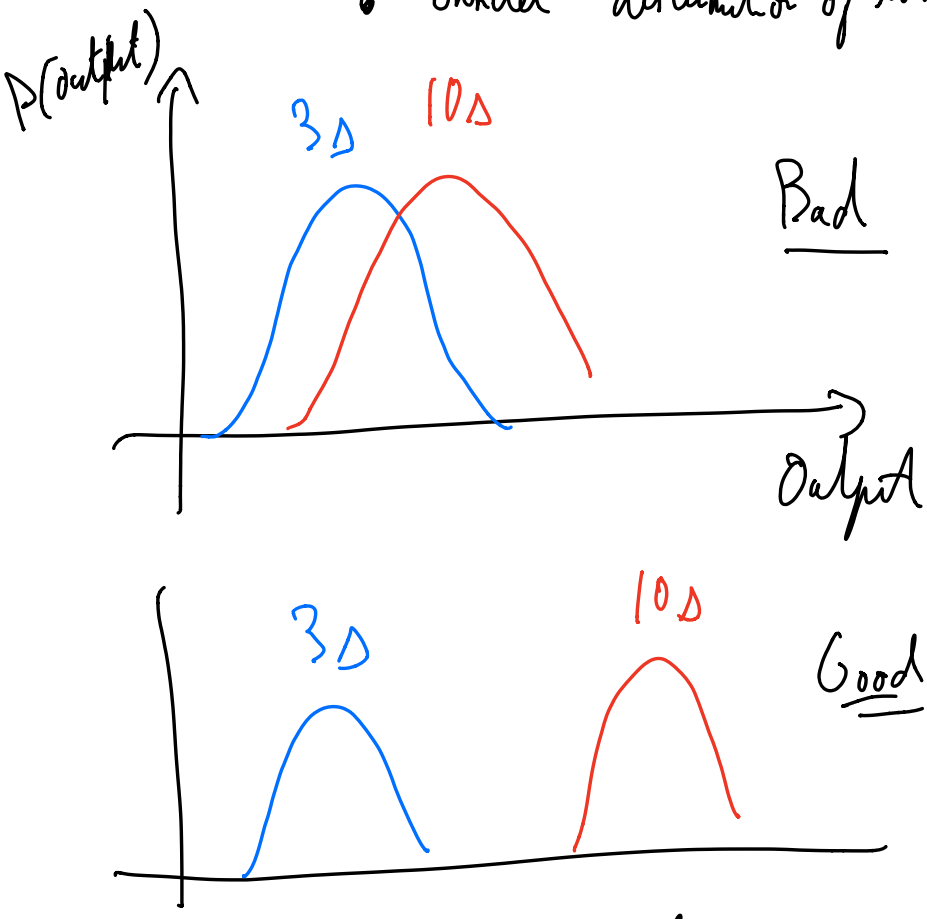
Here fitness quantifies this absolute discrimination

we want "a separation"



One way to do it: • imagine you take random L constructs with # binding times (say 3 or 10s)

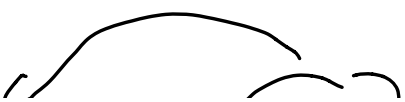
• consider distribution of some output

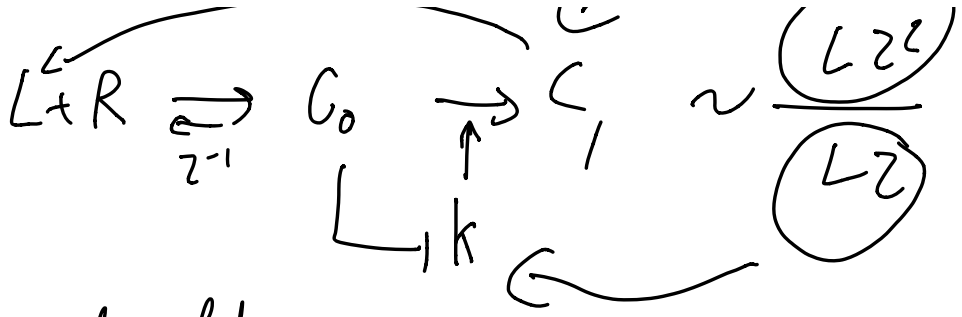


Mutual Info is a way to do this

Results

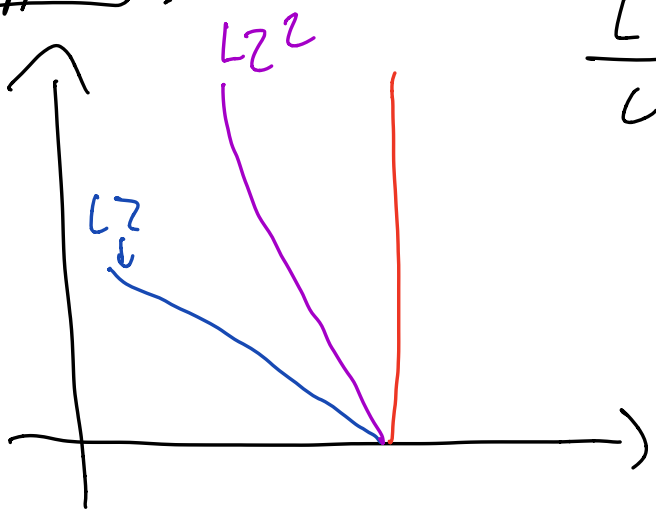
τ^{-1}





Very simple solution

What happens ?



$\frac{LZ^2}{LZ} = (Z)$

↓

you can detect this

Realistic DR curves

Ultra-simple solution but... not so simple

ANTAGONISM

What happens with mixtures

10 anti mAb vs 10^5 mAb

More → WITHIN

Pure ligands $Z_1 > Z_c > Z_2$ (add this)

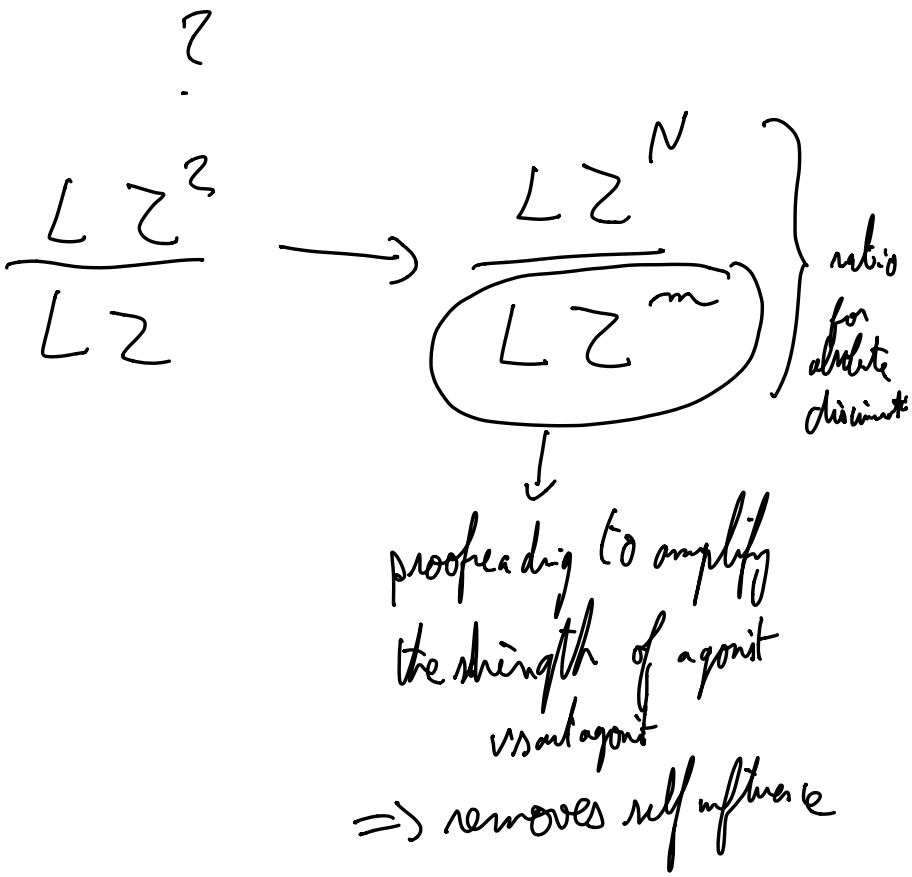
$$\frac{LZ_1^2}{LZ_1} > Z_c$$

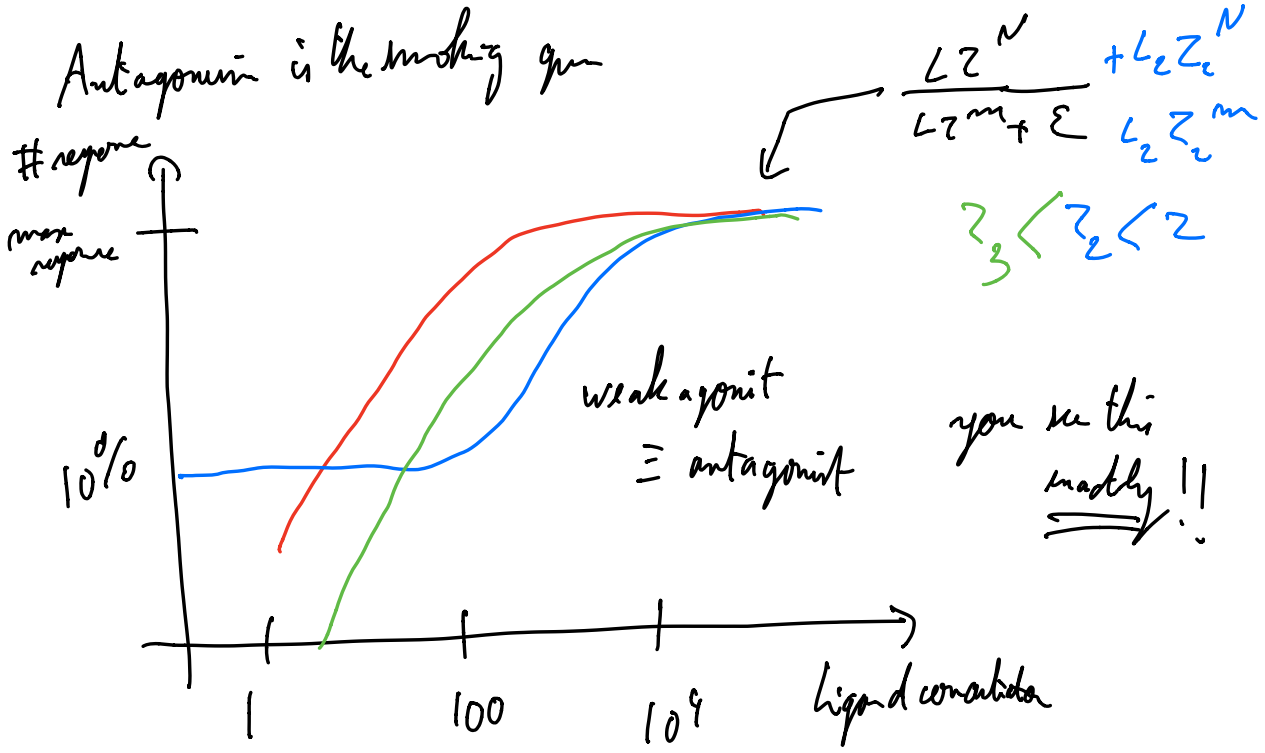
$$Z_1 > \frac{L_1 Z_1^2 + L_2 Z_2^2}{L_1 Z_1 + L_2 Z_2}$$

If enough L_2 ⇒ get lower than threshold

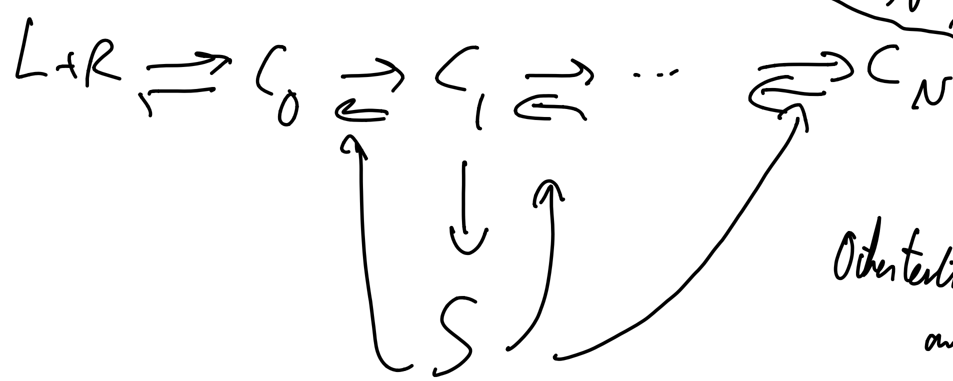
Simple adaptive routing

10^5 mAb at 0.1 s ⇒ kill immune response


?
$\frac{LZ^2}{LZ}$
$\frac{LZ^N}{LZ^m}$
ratio for absolute discrimination
proofreading to amplify the strength of agonist vs antagonist
⇒ removes self influence


Antagonism is the smoking gun
$\frac{LZ^N}{LZ^m + \varepsilon} + L_2 Z_2^N \; L_2 Z_2^m$
$Z_3 < Z_2 < Z$
response
max response
10%
weak agonist ≡ antagonist
you see this madly !!
1
100
10^4
Ligand concentration

More "realistic" model



Central idea: Tug of war LZ^N vs LZ^m

But you could get $h(L)f(Z)$ vs $h^k(Z)g(Z)$

new phenomena

h k mostly linear

but not always

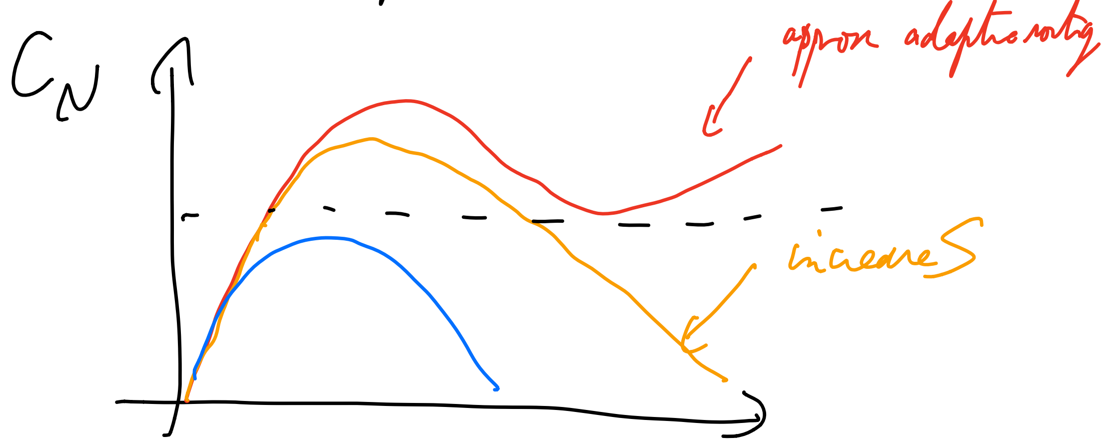
Other tricks: SHP-1 antagonizes other side of the cell

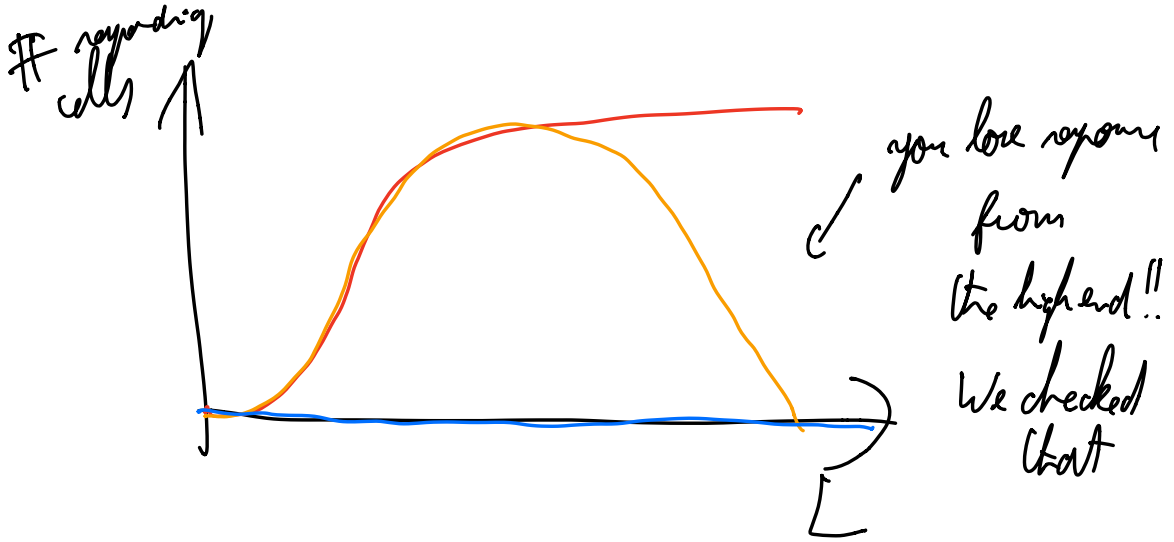
This gives you 2 properties I mentioned:

NMDR

digital vs analog

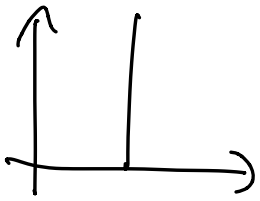
They are related





Can we get rid of antagonism? NO!!

Theorem Absolute discrimination



⇒ antagonism

Why? Assume thresholding of continuous variable

$$T(\{L_i, Z_i\})$$

$$\left.\frac{\partial T}{\partial Z_i}\right|_{Z_0} \geq 0$$

On the line $T(L_1, z_c) = 0$ by definition

Taylor expand on the line

$$T(\{L_i, z_i\}) = T(\Sigma L_i, z_c) + \sum \frac{\partial}{\partial} (L_i, z_c) \, L_i \, (z_i - z_c)$$

$$T(\{L_1, z_c\}; L_2, z_c - dz) \qquad \frac{\partial}{\partial} > 0$$

$$= T(L_1 + L_2, z_c) - dz \, \frac{\partial}{\partial}(L_1, z_c) L_2$$

$$= T(L_1, z_c) - dz \, \frac{\partial}{\partial}(L_1, z_c) L_2$$

$< 0 \Rightarrow$ contraction

linear term, now you can build many $\neq$ models at the non linear order

or:

$$L+R \xrightarrow{K} D \xrightarrow{\mu^{-1}} \phi$$

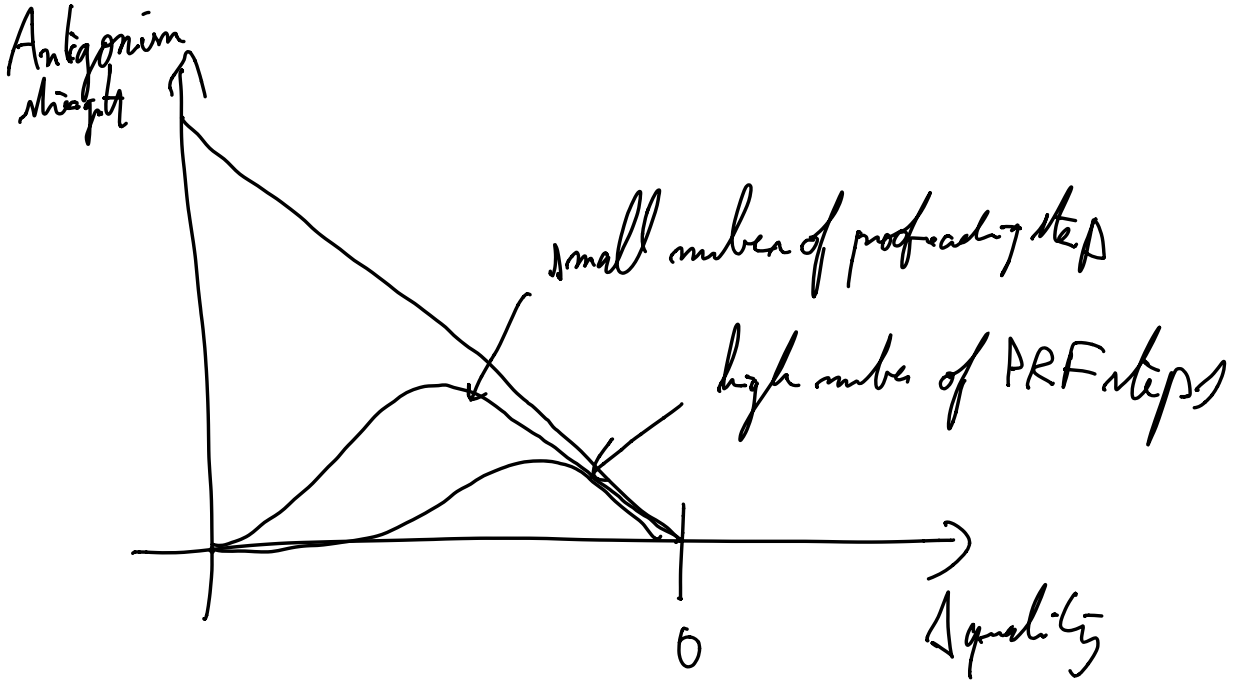
$$\dot{R} = 1 - k \sum L_i R$$

$$\dot{D}_i = k L_i R - \mu_i^{-1} D_i$$

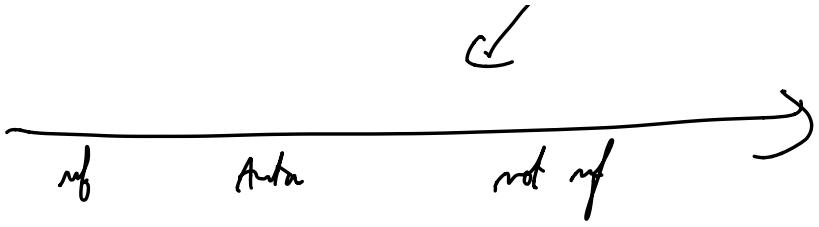
$$\sum D_i = \left(\sum \mu_i L_i\right) R = \frac{\sum \mu_i L_i}{\sum L_i}$$

$\Rightarrow$ average of μ_s

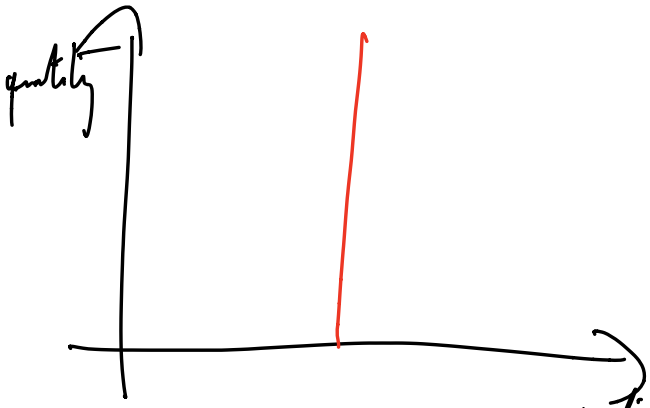
Max antagonism for small μs



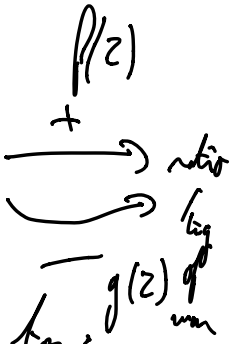
No antagonism off $\Rightarrow$ highly nonlinear and not generic



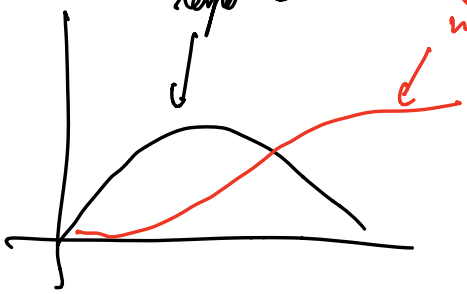
Further



probably very generic theory
("spreading" for ligands)



General tests: via antagonists and/or non monotonic dose response curve



internal negative feedback

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or induced by weaker but more abundant ligands

- Torigoe et al, Science 1998

FC ERIs (other kid of immune receptor)
antagonism via deactivation of kinase =) exactly AS V

- Reduction of model
  - Proulx - Giraldeau et al, Biophys J 2017

Concluding remarks

Evolution or ... computer aided network discovery

- coarse-grained fitnesses
- Many "spandrels" come for free. This is probably the same in nature.
- Simple networks give rise rich dynamics (like also Remistry)
  - hypothesis mechanism

We were kind of lost in the minime haistball, now we have the "good" class of models