LATINR

Integración de datos aplicada a estudios de farmacodinamia

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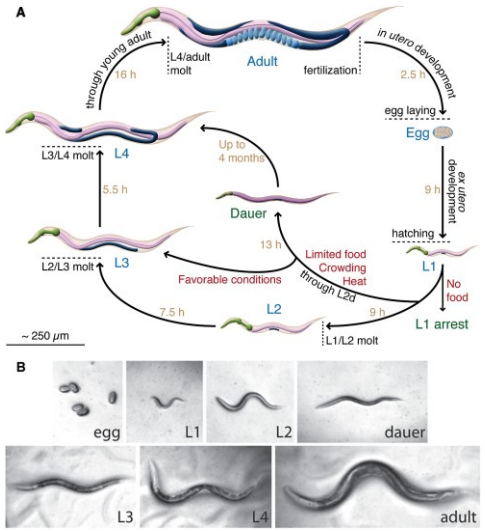
OBJETIVO

Evaluar y cuantificar el grado de sinergismo entre dos fármacos antiparasitarios

1 + 1 =	1 + 1 =	1 + 1 =
1	2	3
antagonismo	Indeferencia	Sinergismo

DOSIS - RESPUESTA



Matriz de datos de 6x6
(2 grupos, 6 niveles por grupo, 25 combinaciones, 2 réplicas)
registradas durante en 980 minutos con una frecuencia de lectura cada 5 minutos.

19109 celdas de datos

Modelo Biológico + Diseño Experimental

Group IVM
[n≠; 0.1 : 1.6 µM]

Group EPM
[n≠4; 0.1 : 1.6 µM]

Groups Matrix IVM:EPM
[n≠4; ratio 0.1:1.6]

Group Control
[n≠4; DMSO 1%]

Egthty (~80) worm the *C. elegans* were alocate in 96 dishes were involved in the following trials:

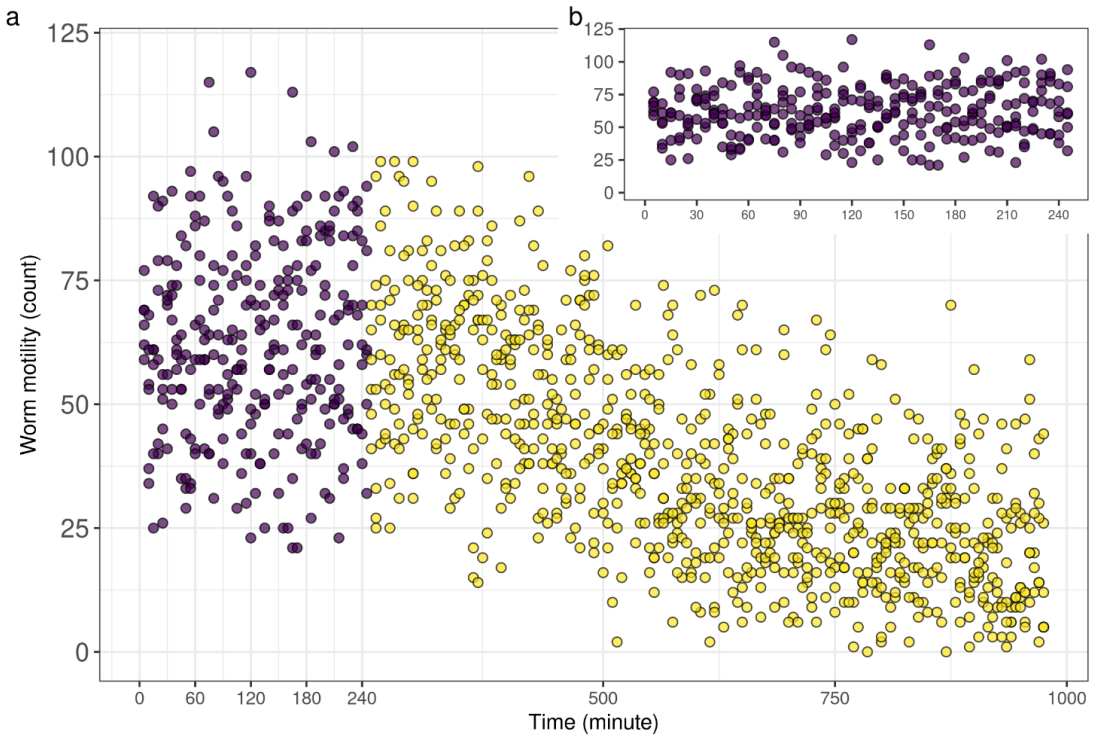
Infrared motility assay were registered up to 980 (240) min and Inhibition of motility activity were determineted

1. EXPERIMENTAL

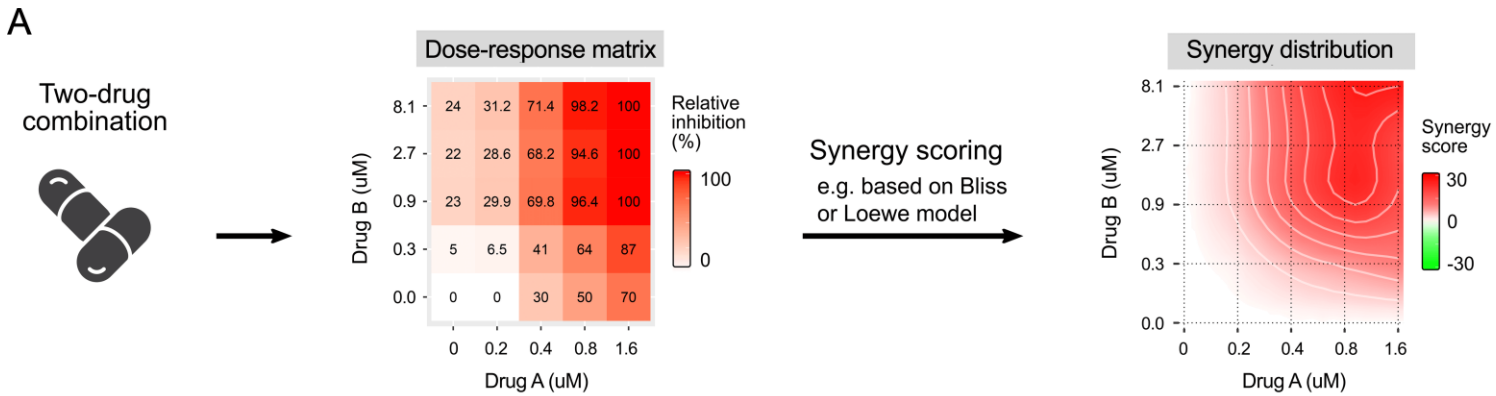
Well	Group/Time[m]	5	10	15	20
A1.0	000_Group0	27	12	29	24
B1.0	001_Group1	8	2	0	7
C1.0	002_Group2	9	8	8	4
D1.0	003_Group3	55	35	14	12
E1.0	004_Group4	20	17	15	17
F1.0	005_Group5	48	49	27	28
G1.0	000_Group0	20	31	32	23

Aplicamos herramientas de limpieza, ordenado y adaptación de los datos, acondicimonado a un formato específico para evaluar modelos farmacodinámicos en un paquete desarrollado

block_id	drug1	drug2	cell_line_name	conc1	conc2	response	conc_unit



2. LIMPIEZA



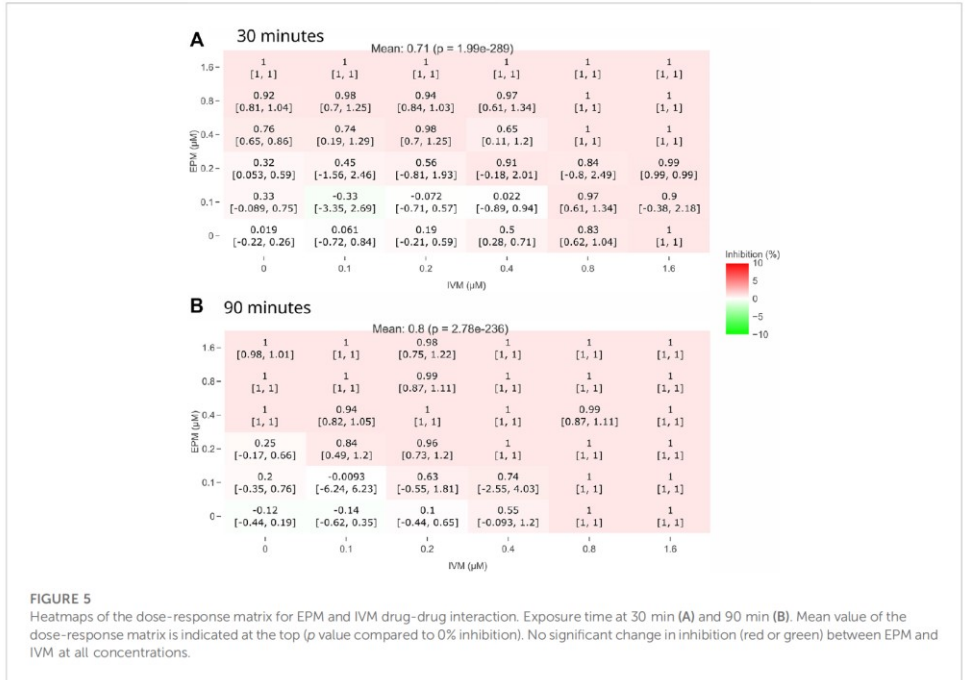


FIGURE 5
Heatmaps of the dose-response matrix for EPM and IVM drug-drug interaction. Exposure time at 30 min **(A)** and 90 min **(B)**. Mean value of the dose-response matrix is indicated at the top (*p* value compared to 0% inhibition). No significant change in inhibition (red or green) between EPM and IVM at all concentrations.

SynergyFinder

-- a FAIR tool for drug combination discovery

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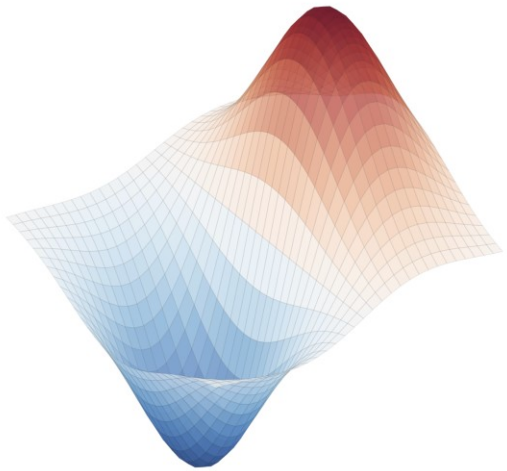

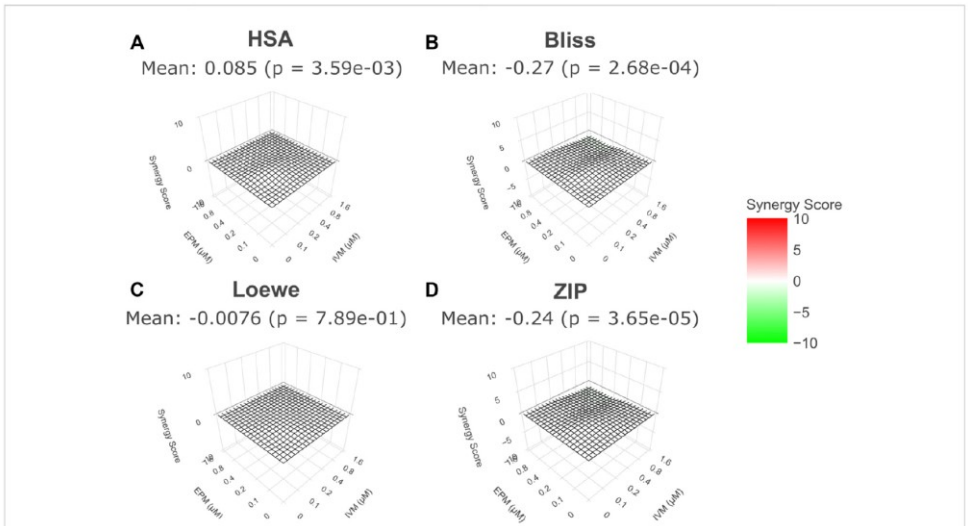

FIGURE 4
3D surface of Synergy Scores for EPM and IVM drug-drug interaction. For all models, EPM and IVM interaction landscapes are shown in 3D **(A)**. Highest Single Agent model (HAS) **(B)**. Bliss Independence model (BLISS) **(C)**. Loewe model (LOEWE) **(D)**. Zero Interaction Potency model (ZIP). 90 min exposure time is shown in all cases. The mean value of Synergy Score is indicated in the SD surface (*p* value compared to 0% inhibition). No significant synergy (red) or antagonism (green) between EPM and IVM at all concentrations.

Procesamos el paquete desarrollado (*Bioconductor project*) y obtuvimos las salidas en la estructura establecida según paquete

3. ANALISIS ESPECÍFICO

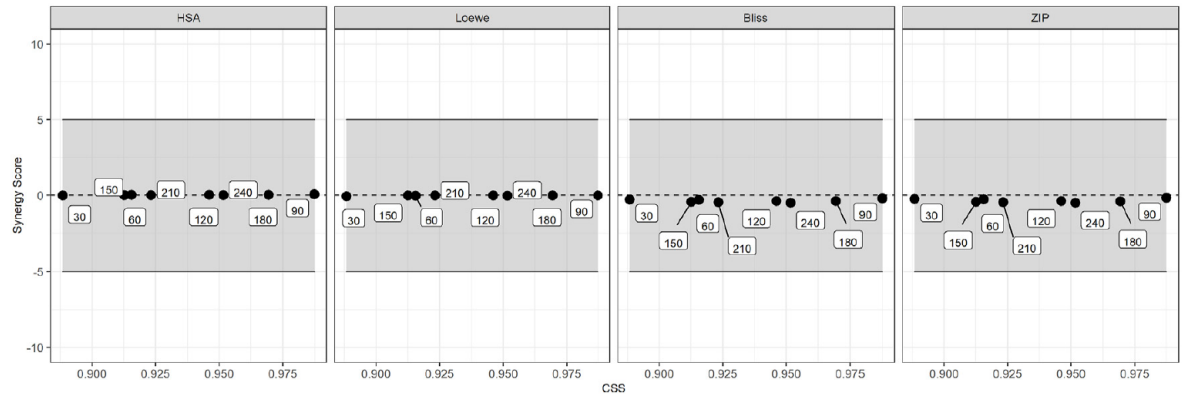

FIGURE 6
Synergy Scores (SS) and the overall Combination Sensitivity Score (CSS) for the combination EPM/IVM matrix. Each panel represents a different reference model of Synergy Scoring models with different assumptions regarding the expected effect (HSA = Highest Single Agent; BLISS = Bliss Independence; LOEWE = Loewe model and ZIP = Zero Interaction Potency). The gray zone indicates additive effect (Malyutina et al., 2019). Squares indicate the different times.

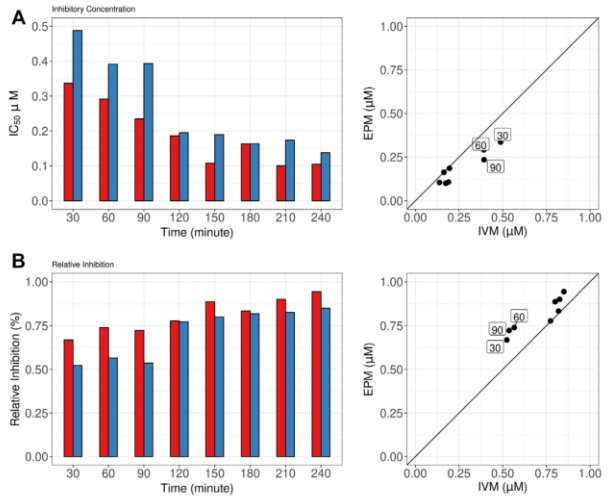

FIGURE 3
Half-maximal inhibitory concentration (IC50) and relative inhibition (RI) for single drugs. **(A)**. Eprinomectin (EPM) and Ivermectin (IVM) IC50 (left) and IC50 EPM/IVM ratios (right). 30–240 min exposure times are shown **(B)**. EPM and IVM RI (left) and EPM/IVM RI ratios. 30–240 min exposure time are shown. The squares highlight the higher potency of EPM than IVM at 30, 60, and 90 min.

Retomamos las salidas de los datos y personalizamos la visualizacion e interpretación de la información

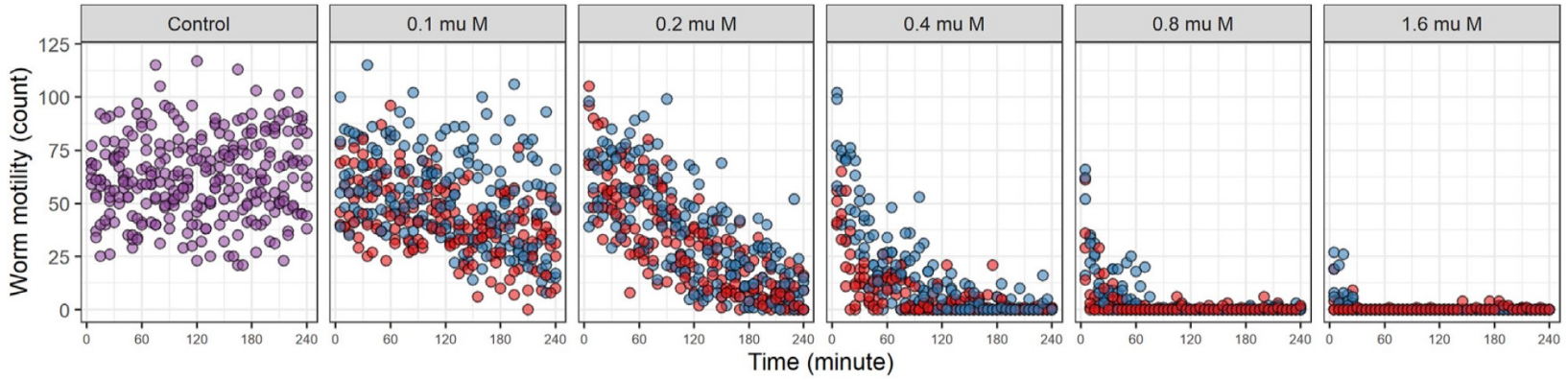

FIGURE 2
Locomotive activity for drugs alone. Worm motility over time was registered for 240 min. Different drug dose was used (range of 0.1–1.6 μM). Eprinomectin is depicted in red, Ivermectin in blue and Control in purple.

4. PERSONALIZACIÓN

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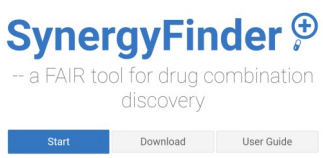
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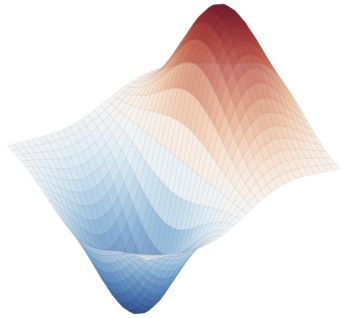

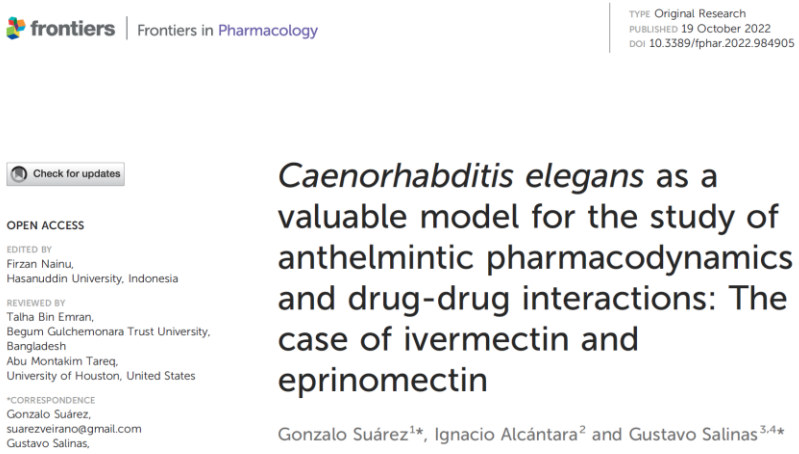
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Caenorhabditis elegans as a valuable model for the study of anthelmintic pharmacodynamics and drug-drug interactions: The case of ivermectin and eprinomectin
Gonzalo Suárez[1]*, Ignacio Alcántara[2] and Gustavo Salinas[3,4]*


Repository