Characterizing Activity Landscapes Using an Information-Theoretic Approach

Veer Shanmugasundaram & Gerry Maggiora
Computer-Aided Drug Discovery
Pharmacia Corporation, Kalamazoo, MI

What are Activity Landscapes?

- **Activity landscapes are abstract surfaces drawn on chemistry space containing compounds where the height represents biological activity.**

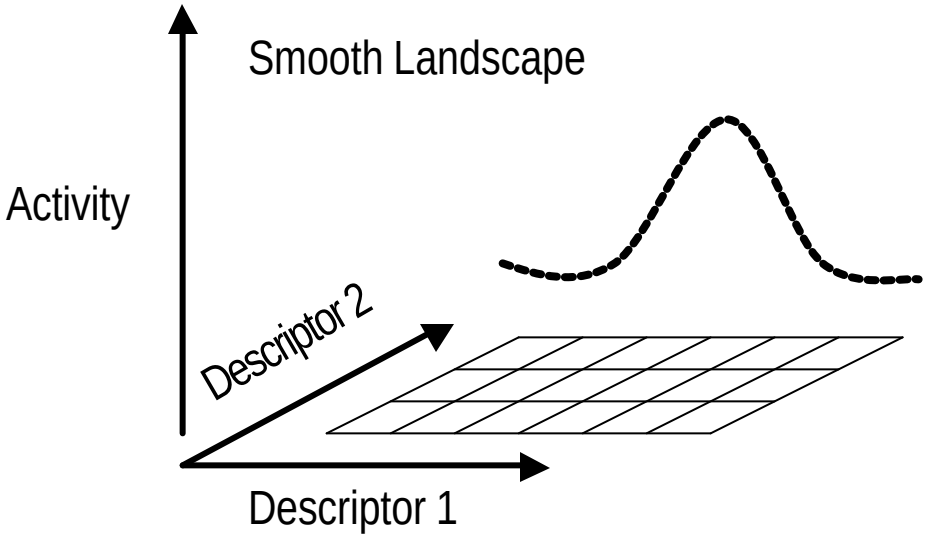
- **Gentle rising hills of activity represent smooth landscape where small structural changes produce gradual changes in activity.**

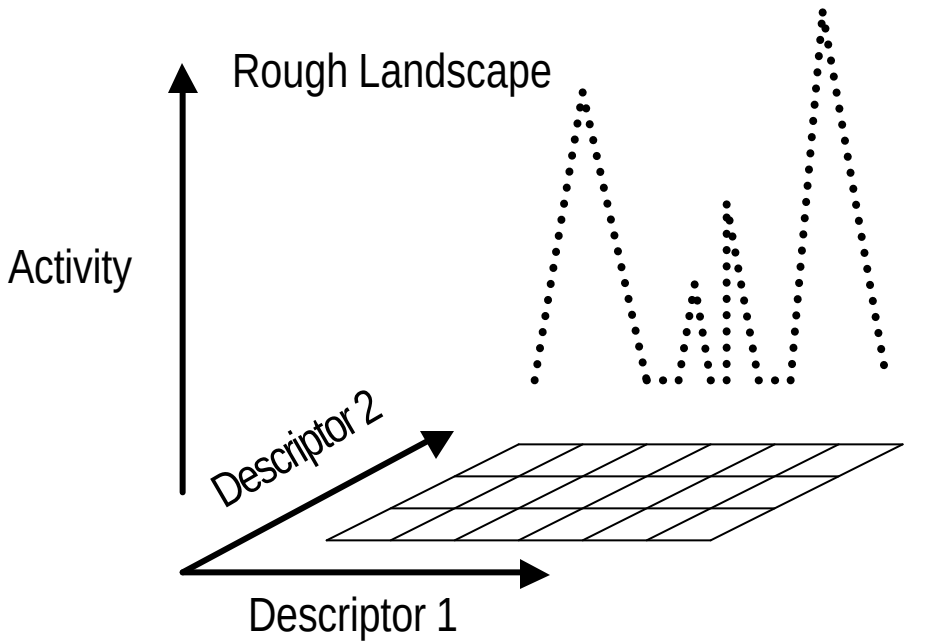
- **Rough activity landscapes are characterized by cliffs where small changes in structure lead to large changes in activity.**

Smooth Landscape - Flint Hills, Kansas

Rough Landscape - Bryce Canyon, Utah

Why do we need to characterize them?



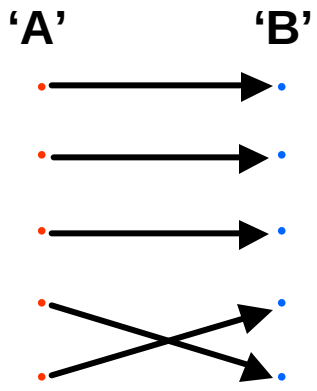


- **What should be the minimum size of a representative dissimilarity subset of the corporate collection? Is it assay dependent?**
- **Develop “stopping-rules” to assess “have we screened enough?”**
- **Comparing activity landscapes of different biological targets.**

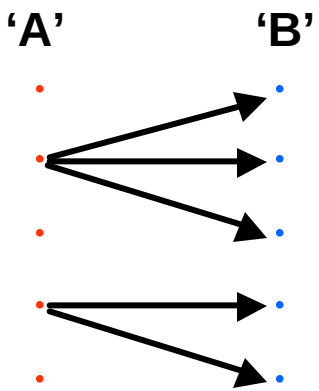
Shannon's Theory of Communication

Transmission of Messages

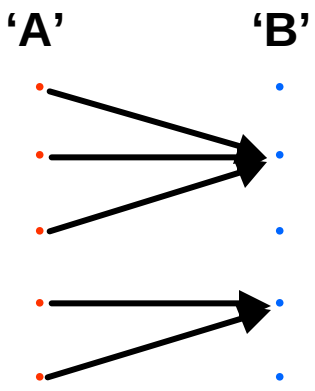
'Perfect' Mapping



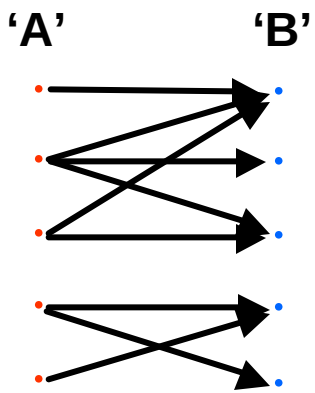
'Noisy' Mapping



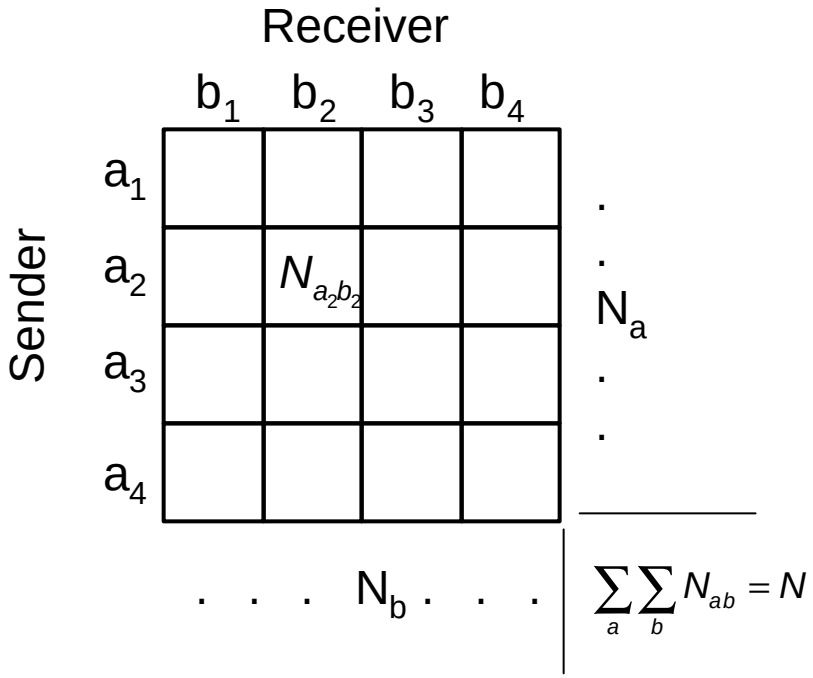
'Equivocal' Mapping



'Mixed' Mapping

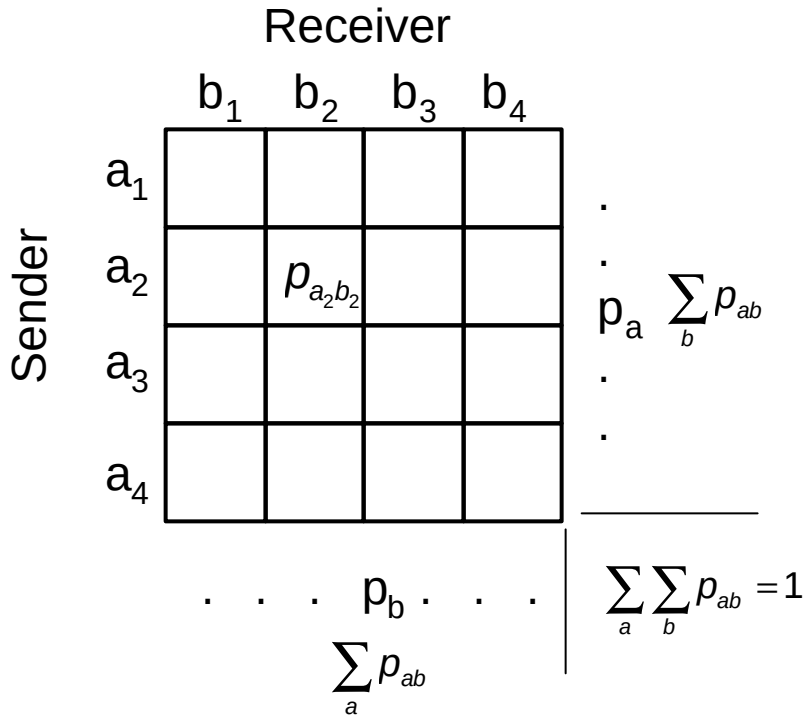


Shannon's Theory of Communication



- Probabilities or frequencies with which messages are sent.
- How each sent message is received.
- Probabilities or frequencies with which messages are received.
- How each received message was sent.

Shannon's Theory of Communication

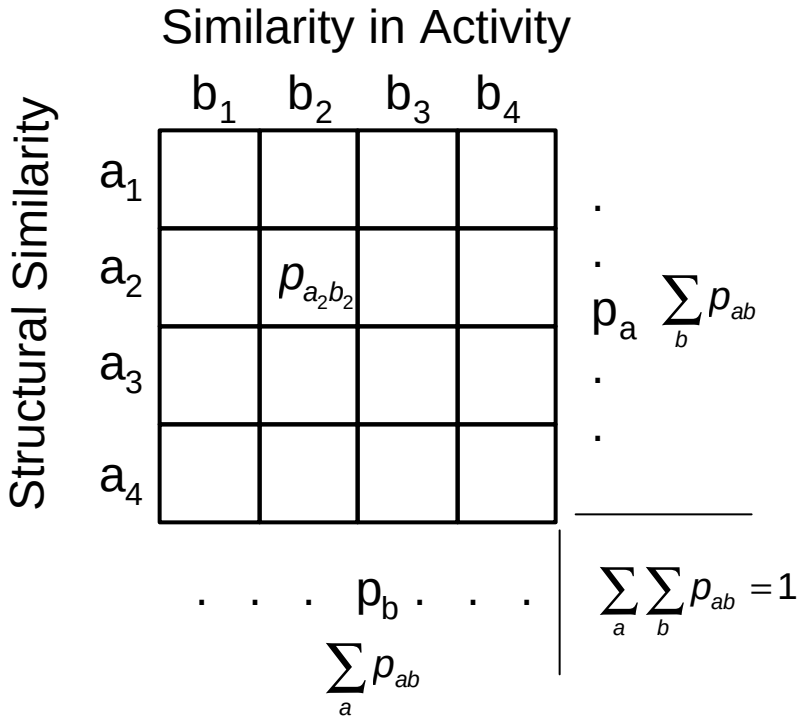


Shannon's entropy $H(X) = -\sum_x p_x \log_2 p_x$

$H(A) = -\sum_a p_a \log_2 p_a$ $H(B) = -\sum_b p_b \log_2 p_b$ $H(AB) = -\sum_a \sum_b p_{ab} \log_2 p_{ab}$

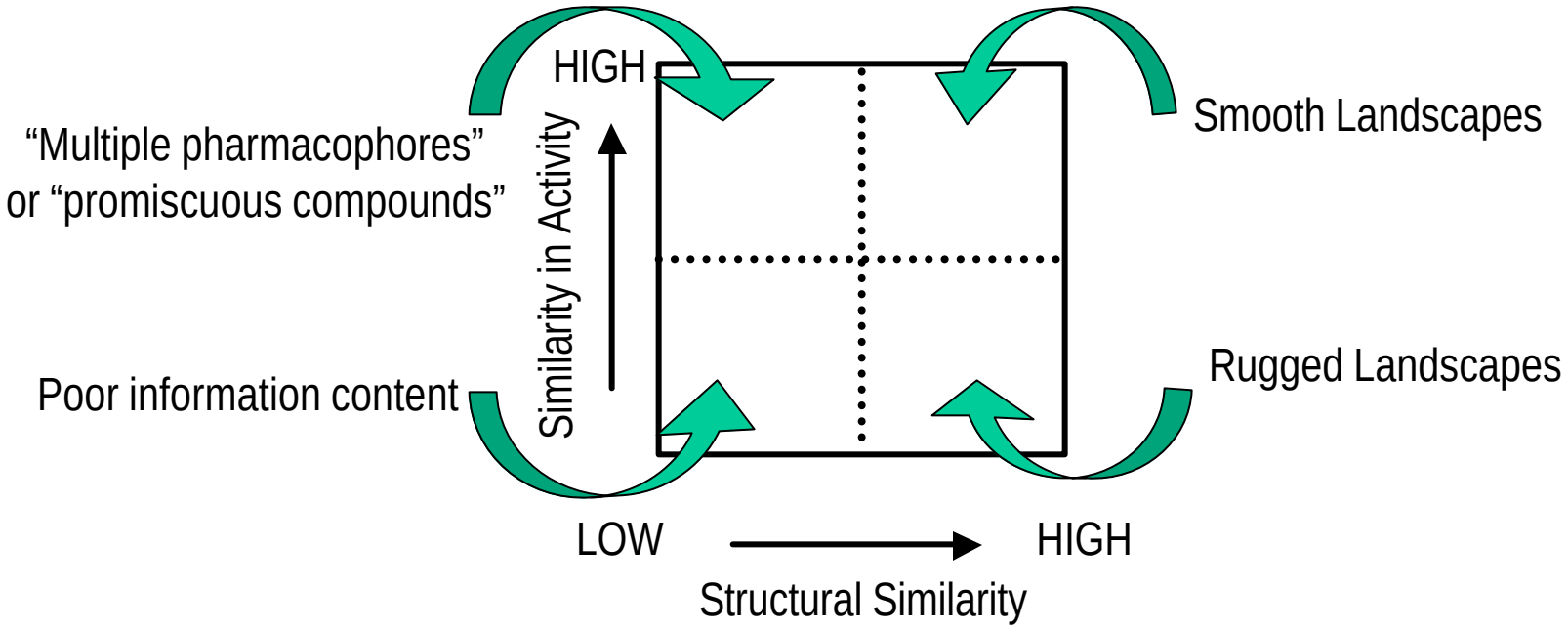
Sender's entropy Receiver's entropy Joint entropy

Structure - Activity Mapping



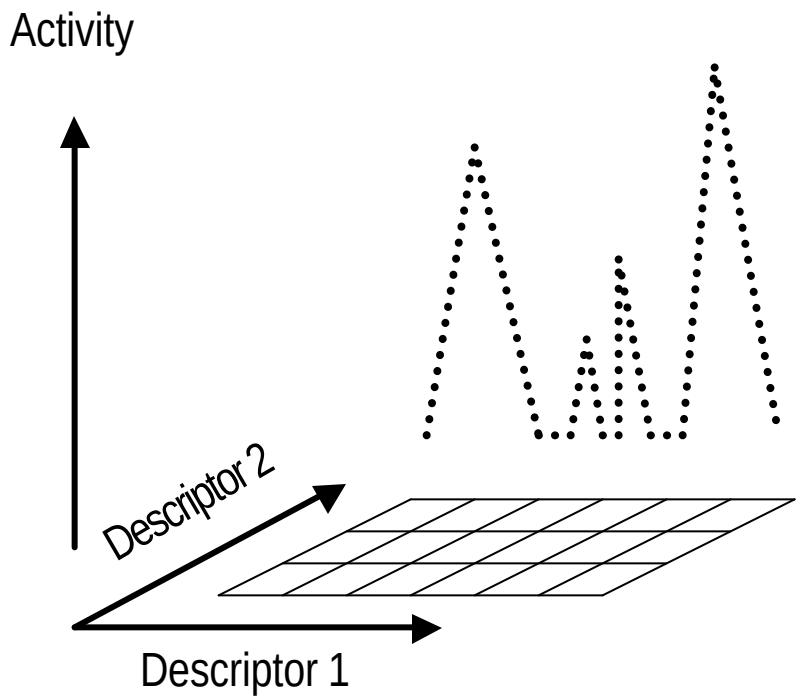
- Structural similarity - Tanimoto similarity (S_{ij}) or inter-compound distances in chemistry space.
- Activity similarity can be defined such that compounds that have similar IC_{50} or % inhibition values have a high similarity in activity.

Structure - Activity Similarity Map

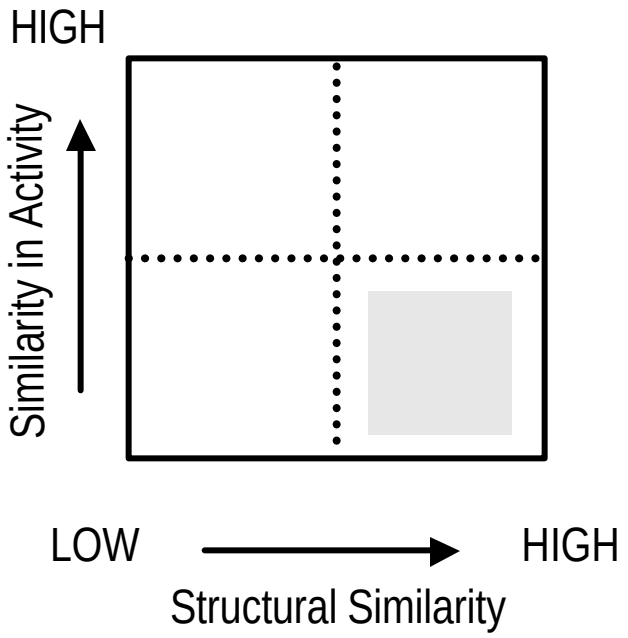


Structure - Activity Similarity Map

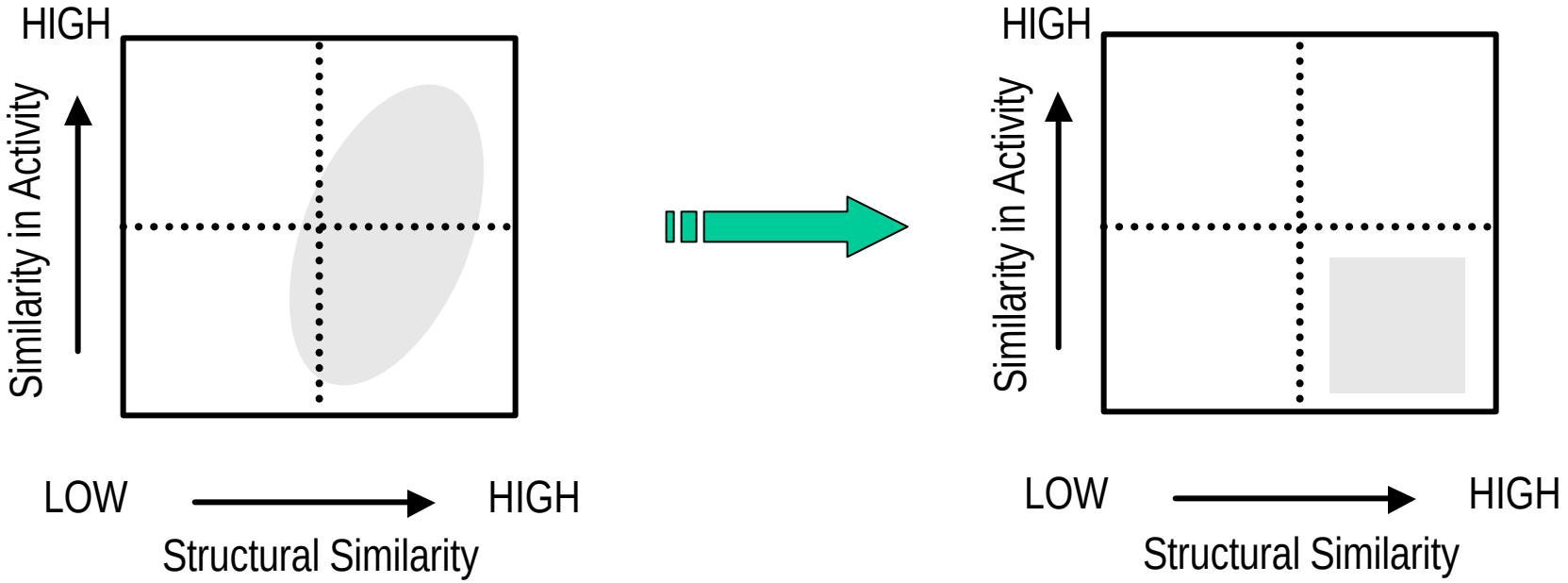
Rough Activity Landscape



Rugged Regions in Similarity Map



Information theoretic measure



Kullback-Leibler information theoretic measure could be used as a global index to characterize the topographic character of activity landscape and to compare the similarities between two different structure-activity maps.

Kullback-Leibler Index

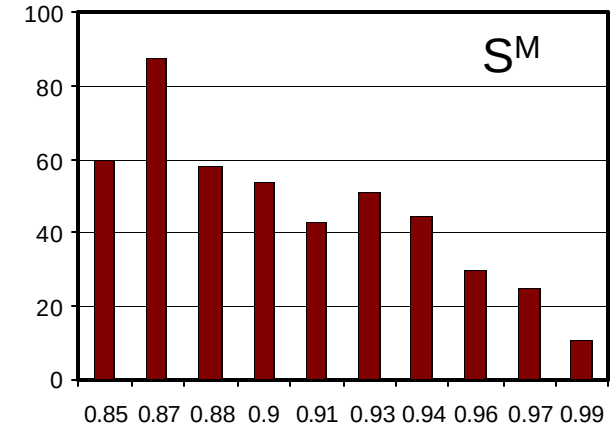
$$D(\mathrm{p}||\mathrm{q}) = \sum_{x \in X} p(x) \log \frac{p(x)}{q(x)}$$

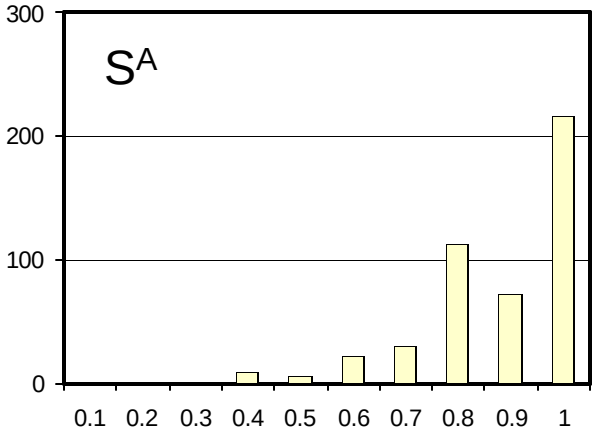
$$0 \log \frac{0}{q} = 0 \qquad p \log \frac{p}{0} = \infty$$

- Kullback-Leiber index is always non-negative.
- Index is zero, if and only if p=q
- Not a true “distance” - not symmetric and does not satisfy the triangle inequality.

Biological Assay 1

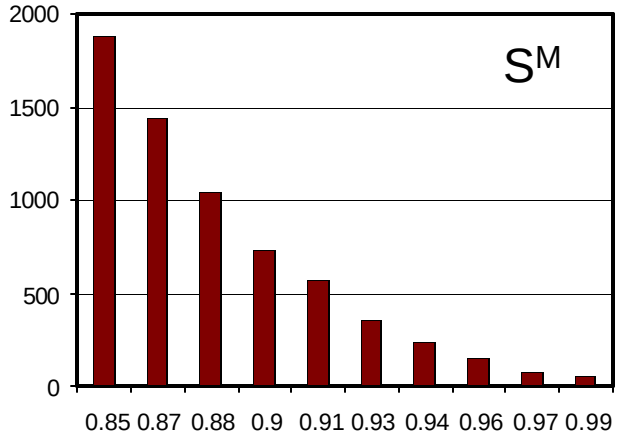
180 cpds
16110 comparisons
465 ($S^M \geq 0.85$)

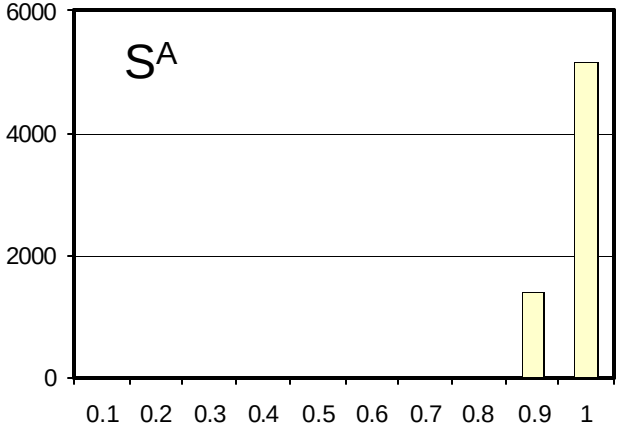




Biological Assay 2

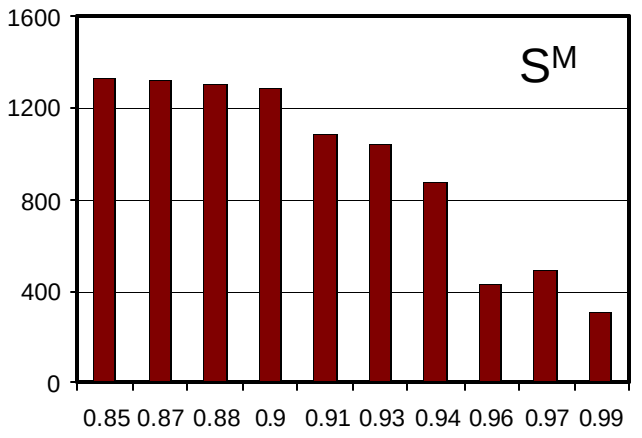
582 cpds
169071 comparisons
6569 ($S^M \geq 0.85$)

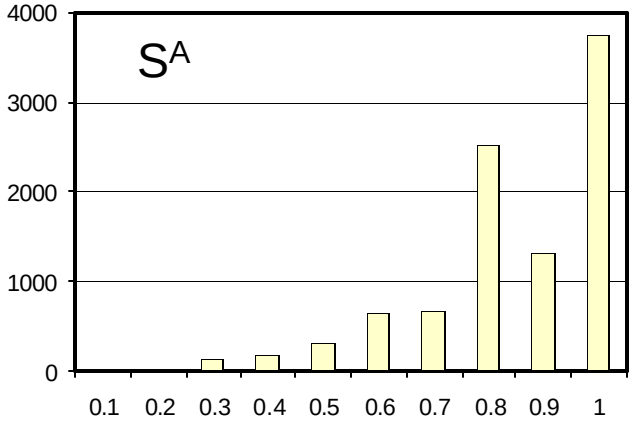




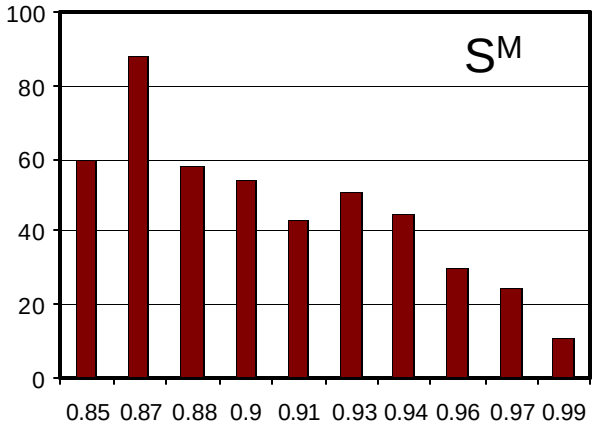
Biological Assay 3

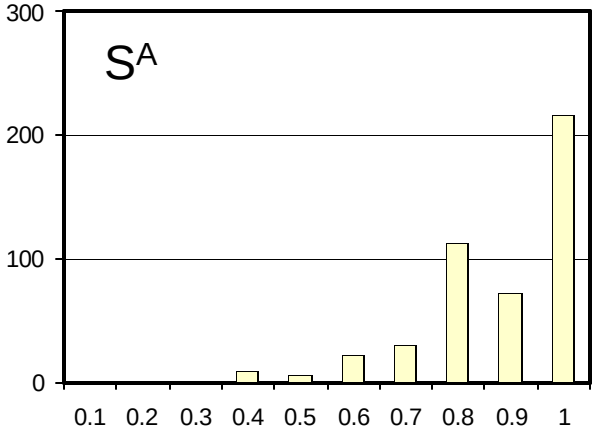
190 cpds
17955 comparisons
9508 ($S^M \geq 0.85$)

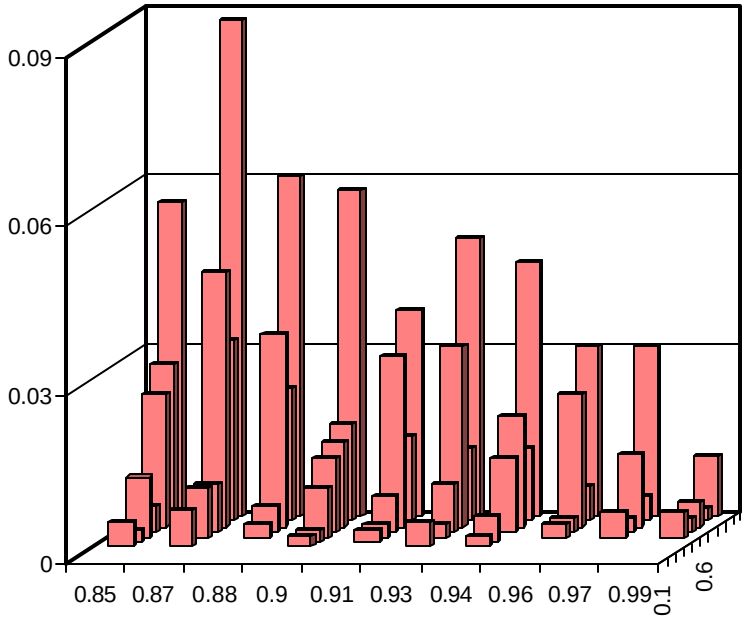




Biological Assay 1



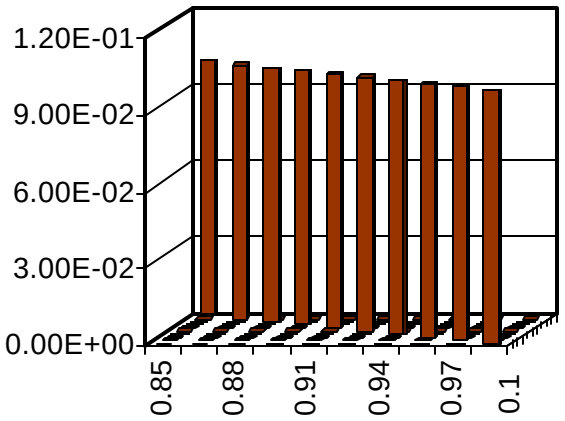




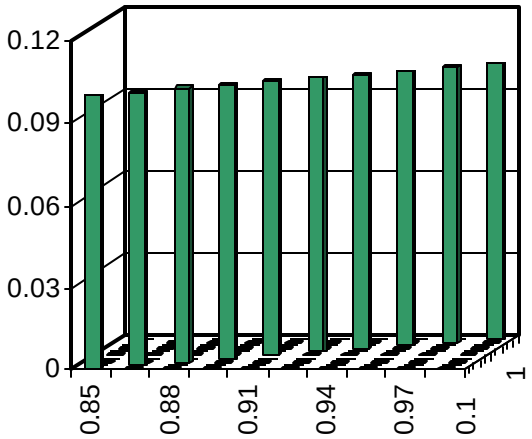
S^A

S^M

Biological Assay 1

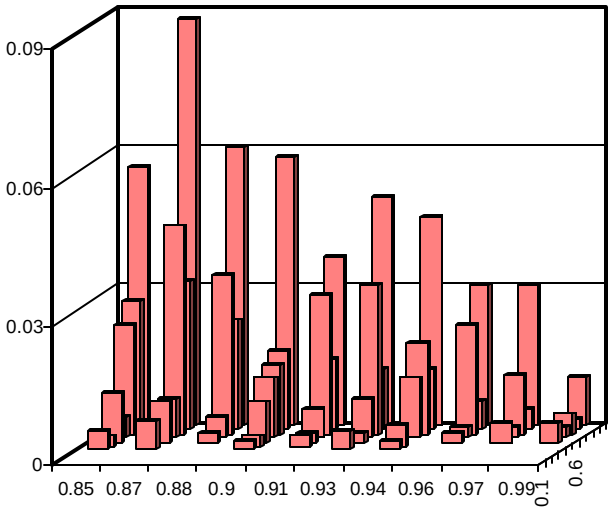


Similarity Map of an Idealized Rough Landscape



Similarity Map of an Idealized Smooth Landscape

Similarity Map of Assay 1



S^A

S^M

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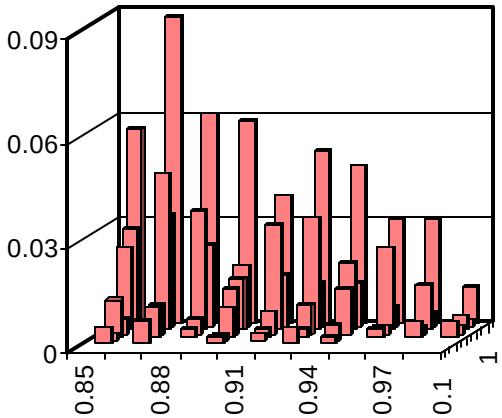

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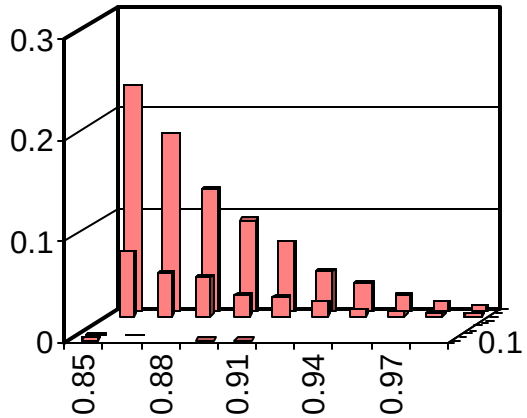

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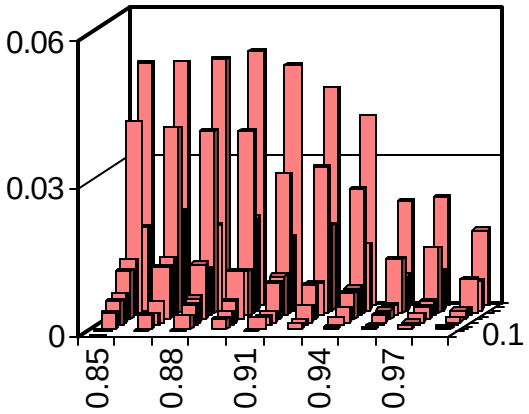

DISTANCES TO IDEALIZED LANDSCAPES	ASSAY 1	ASSAY 2	ASSAY 3
SMOOTH	9.59	9.39	9.57
ROUGH	10.68	12.96	10.36

Summary

- Activity landscapes tend to have smooth and rugged regions.
- Kullback-Leibler information-theoretic index can be used to measure the similarity of a given activity landscape to smooth and rough landscapes.
- If activity landscapes are like Bryce Canyon, we need to sample chemistry space more thoroughly to identify important peaks of activity.